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MedCACpresentations@cms.hhs.gov

RE: Analysis of Coverage with Evidence Development (CED) Criteria

Haystack Project appreciates the opportunity to communicate its recommendations and concerns with the Centers for Medicare & Medicaid Services' (CMS') Coverage with Evidence Development (CED) study criteria to the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC). We urge MEDCAC members to ensure that our patient protection and access concerns are not only considered, but openly discussed within the MEDCAC's public deliberation on February 13-14, 2023.

Haystack Project is a 501(c)(3) non-profit organization enabling rare and ultra-rare disease advocacy organizations to highlight and address systemic access barriers to the therapies they desperately need. Our core mission is to evolve health care payment and delivery systems toward spurring innovation and quality in care toward effective, accessible treatment options for Americans living with rare or ultra-rare conditions. Haystack Project is committed to educating policymakers and other stakeholders about the unique circumstances of extremely rare conditions with respect to product development, commercialization, and fair access to care.

In addition, Haystack Project has a Rare Cancer Policy Coalition (RCPC) that brings together rare cancer patient organizations. RCPC gives participants a platform for focusing specifically on systemic reimbursement barriers and emerging landscape changes that impact new product development and treatment access for rare cancer patients. It is the only coalition developed specifically to focus attention on reimbursement, access, and value issues across the rare cancer community. Working within the Haystack Project enables RCPC participants and rare and ultra-rare patient advocates to leverage synergies and common goals to optimize advocacy in disease states where unmet need is high and treatment inadequacies can be catastrophic.

A significant proportion of Haystack Project's advocacy and education efforts focus on identifying and drawing attention to the unintended consequences our patient communities suffer when policy initiatives and process refinements fail to consider the unique challenges associated with rare and ultra-rare conditions. Our comments:

- Provide a brief summary of challenges associated with developing and accessing rare disease treatments and the significant potential for CED processes and criteria to disproportionately harm patients with extremely rare conditions,

- Outline important contextual concerns and overarching patient protection considerations that fall outside of CMS' narrow remit to the MEDCAC, and

- Communicate our recommendations on specific CED study requirements included in and omitted from the MEDCAC voting questions.

Background

Innovation in how we understand and address disease mechanisms has advanced at a pace that would have been unthinkable decades ago. Targeted cancer treatments, gene therapy and regenerative medicine, and immunologic approaches to rare, serious, and life-threatening conditions give renewed hope to the millions of Americans affected by a rare disease. However, exceedingly small populations, long diagnostic journeys, and a limited natural history knowledge base for many rare diseases 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. These patients and their providers often face a labyrinth of claim denials, prior authorization requirements, reconsiderations, and appeals to access the care they need. Coverage policies and mechanisms, particularly those within Medicare National Coverage Determinations, can present absolute, impenetrable, and persistent barriers to access if they are implemented without considering the treatment needs of rare disease patients.

Haystack Project and the patient advocacy organizations within its membership continue to believe 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. In addition, we have significant concerns that refinements to CMS' CED study criteria could further compromise care access for Medicare's rare disease population. The MEDCAC and its members are uniquely positioned to alert CMS to potential unintended harms for rare disease patients and advise the Agency on whether and how it can adapt the CED framework and study criteria to be "fit for purpose" within the context of very rare conditions.

- 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. 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 process foreclosed. ***These factors drive increased scrutiny and create a perception of evidentiary uncertainty likely to trigger CED. The need to utilize these approval mechanisms, together with limited treatment alternatives, however, make it particularly inappropriate, and potentially unethical, to condition access on participation in a randomized clinical trial.***

- Most individuals living with a very rare condition rely on off-label treatments to reduce disease burden and/or slow disease progression. ***Unless CED mechanisms and study criteria expressly provide for or exempt off-label uses supported by evidence in very rare conditions, any NCD requiring CED would completely foreclose access to treatment in these patients.***

- 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. ***A clear, robust, and meaningful informed consent requirement is, therefore, even more important than it is when study participation is not a structured "gatekeeper" to treatment access.***

MEDCAC should incorporate contextual factors and overarching patient protection considerations into its analysis, deliberation, and recommendations.

The CED process was implemented in 2005 with the stated goal of generating data so that CMS could verify the appropriateness of an item or service, consider future changes in coverage for its use, and improve the evidence base for or against the use of an item or service. AHRQ's report described CED as "a National Coverage Determination (NCD) that allows patients to access these select medical items and services, with coverage, on the condition that there is prospective collection of agreed upon clinical data."

Haystack Project is concerned that the CED study criteria lack the flexibility to resolve the persistent concern that CED has been ineffective in both enabling beneficiary access and generating the data CMS seeks. Since the 2005 implementation of CED, 27 CED determinations have been initiated and just 6 have resulted in an NCD removing the CED requirements. Any revision to CED study criteria should address CED deficiencies in encouraging participation from

study sponsors, investigators, and patients. Put simply, the revised criteria should make CED studies ***less*** burdensome and costly for industry, providers, and patients.

Similarly, we urge the MEDCAC to recognize that well-considered recommendations on aspects of Medicare coverage require a holistic view of issues and their contextual impact. Like AHRQ, the MEDCAC was asked to provide recommendations on a very narrow piece of the CED paradigm – what study criteria would likely ensure that CED studies generate strong evidence on health outcomes. AHRQ understood that its mission was to recommend requirements that would "guide investigators to collect and use data generated in the care of patients to produce strong evidence about the health outcomes … with integrity in the scientific process and transparency at all stages." We recognize that any inquiry seeking recommendations to facilitate robust, valid, reliable data would result in a set of criteria similar to AHRQ's recommendations presented to the MEDCAC for consideration and voting. A uniform set of clinical study requirements likely furthers CMS' interest in generating scientifically valid data. It does not, however, address the inherent ethical, logistic, and health equity concerns that CED injects when applied to divergent technologies that address disparate disease states and have been subjected to varying degrees of FDA review and oversight.

Context is important. Lack of contextual analysis has likely created the considerable tension between an access-enabling view of CED that facilitates innovation and one that leverages Medicare's beneficiaries as research subjects to satisfy an amorphous bar of certainty on whether an intervention is reasonable and necessary. Viewed within the contextual realities that Medicare beneficiaries face, it is unlikely that the question of "how can Medicare ensure that payments are not made for interventions that are not medically necessary?" would be answered with a one-size-fits-all mechanism conditioning beneficiary access on participation in randomized, double-blinded clinical trials.

Moreover, as we expressed to AHRQ, we have substantial concerns that directing CED at FDA-approved therapies transforms a coverage mechanism into an inflexible utilization management tool. Beneficiaries become research subjects, and treatment "decisions" are subjected to randomization and even "blinding" on the precise intervention. CED does not simply enable access to promising treatments. Used in the context of FDA-approved drugs, it conditions access to safe and effective treatments on factors beyond the control of patients and their treating providers (clinical trial availability, eligibility, and randomization). It also conditions access on beneficiary willingness to place their care into the hands of researchers rather than the clinicians managing their condition(s).

We urge that MEDCAC make its recommendations on CED study criteria based on full consideration of the contextual variability in Medicare coverage and the need to balance evidentiary certainty with Medicare beneficiary access to care and the ethical conduct of research on human subjects.

Recommendations on specific CED study requirements included in and omitted from the MEDCAC voting questions.

Each CED NCD and its study questions, priority outcomes, data thresholds (and other structures) constitute research on human subjects requiring review by a central Institutional Review Board.

Haystack Project agrees that granularity, certainty and transparency from CMS on clinical study requirements and the research questions that those studies must resolve are essential to any successful CED mechanism. We are, however, concerned that any entity (including CMS) 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, in and of itself, conducting research.*** CMS and AHRQ review and approve study protocols, gather and review data on patient outcomes, and assess study results. Although including a requirement that each CED study be reviewed by an Investigational Review Board (IRB) is important, 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. The Common Rule 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 payment for benefits, the clearly articulated intent of the exemption is to allow government agencies to broadly examine the effectiveness of their policies and programs – not to conduct controlled clinical trials examining the impact that a particular intervention has on Medicare patient health outcomes. Haystack Project's understanding is bolstered by the fact that the regulation references 1115 waivers and the HHS flow chart references procedures.

We urge MEDCAC to recommend a requirement that CMS obtain a clear and specific assessment of the ethical and patient protection concerns associated with each CED NCD and that it 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 an FDA-approved treatment used within its labeled indication or in a manner supported by evidence when used off-label for oncologic and rare disease patients. The requirement is even more imperative when the subject treatment addresses a life-limiting, progressive, and/or potentially fatal condition and access will be conditioned on study participation.

Finally, 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.

Haystack Project urges MEDCAC to discuss and recommend inclusion of the requirement that "investigators obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data, unless an institutional review board deems it to not be human subjects research or eligible for waiver or alteration of consent"

AHRQ had included the above requirement in its draft report but deleted it from the final report provided to the MEDCAC. AHRQ's rationale was that "[a]fter discussion with the KI [key informant] Panel, this requirement was deemed unnecessary, as Institutional Review Board includes informed consent requirements." It appears that AHRQ also removed the informed consent language from its revised IRB requirement and then omitted the revised IRB requirement from the study criteria submitted to MEDCAC. Haystack Project is unaware of any public policy rationale for declining to require informed consent for participation in a clinical study evaluating the impact of an intervention on health outcomes. Moreover, we believe that even if such a requirement were not strictly necessary for a specific CED study, its inclusion would further the public trust in CMS-required clinical studies as a condition of coverage.

We strongly urge MEDCAC to recommend informed consent requirements that protect beneficiaries ***as patients***, including:

- 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
- Whether research subjects will be able to access treatment outside the clinical trial and 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
- Availability of the FDA-approved treatment for individuals unwilling to accept the risk of randomization to the control arm and able to find alternative funding
- 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

Deletion of the requirement that "when relevant, investigators follow best practices for establishing and maintaining a registry" creates ambiguity on whether CMS has abandoned use of CED registries in favor of controlled clinical trials."

The Haystack Project is concerned that the study criteria recommendations from AHRQ appear to eliminate the registry pathway in CMS' CED NCDs. AHRQ's rationale for eliminating the requirement was that "[t]he KI Panel noted that there could be confusion about whether the requirement refers to establishing a registry to meet a CED requirement or conducting a "registry study." Moreover, since establishing a registry does not generate evidence without an accompanying study design, and since other requirements cover study design, this requirement was deleted." Neither the original requirement nor the AHRQ revision are included in the MEDCAC voting panel questions. We urge that MEDCAC and/or CMS clarify which of the AHRQ-recommended requirements excluded from the MEDCAC voting questions are to be included in CMS' clinical study criteria.

CED is likely to perpetuate and exacerbate health inequities despite implementation of AHRQ's recommended new requirement that "[t]he study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended users of the intervention. This includes attention to the intended users' racial and ethnic backgrounds, gender, and socio-economic status, at a minimum"

Haystack Project recognizes that the challenges in enrolling racially and ethnically diverse populations in clinical trials 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 health care 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 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, 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. It also negates the critical element of informed consent that researchers have historically denied to Black patient populations

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 are concerned that 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. Specifically, Haystack Project is concerned 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 for inclusion in CED clinical study criteria.

Haystack Project asks that the MEDCAC discuss and consider recommending adoption of additional CED process 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) in a manner generally sufficient for claim-specific payment by a Medicare Administrative Contractor (MAC).

- 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 use within the FDA-approved labeled indication or a medically accepted off-label use.

- 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.

- Adopting CED recommendations, including study criteria, that preserve patient access to off-label use of FDA-approved treatments that are otherwise subject to CED, when the off-label use is medically accepted for a cancer indication or in treating a rare disorder with limited alternative treatment options.

Conclusion

Haystack Project appreciates the opportunity to communicate its concerns and recommendations to the MEDCAC. Patients with rare conditions rely on the hope that research and development efforts will bring treatment innovations that reduce the burden these conditions exact. We urge the MEDCAC to take a holistic approach to the CED study criteria that prioritizes beneficiary access and maintains the protections extended to individuals participating in scientific research studies.

Please contact Haystack Project's policy consultant, Kay Scanlan, at 410-504-2324 or kay.scanlan@haystackproject.org with any questions.

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