HAYSTACK PROJECT
The Voices of Rare & Ultra Rare

September 28, 2022

Dr. Robert Otto Valdez
Director
Agency for Healthcare Research and Quality
5600 Fishers Lane
Rockville, MD 20857

Re: Draft Analysis of Requirements for Coverage with Evidence Development

Dear Director Valdez:

Haystack Project appreciates the opportunity to respond to the Agency for Healthcare Research and Quality's (AHRQ's) Topic Refinement Regarding its Draft Analysis of Requirements for Coverage with Evidence Development (CED) (Draft Report).[i]

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.

The Rare Cancer Policy Coalition (RCPC) is a Haystack Project initiative 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.

Advances in research and development such as regenerative medicine, gene therapy, and other targeted therapy innovations offer a renewed hope that a treatment could be on the horizon for any disease, no matter how rare. Unfortunately, our optimism is tempered by increasing discussions about whether payers -- public and private -- will be willing and able to pay the cost of these highly-targeted treatments. Any National Coverage Decision inquiry on a new FDA-approved treatment can have tremendous consequences for individuals with extremely rare conditions. Patients within a new treatment's labeled indication fear delays in coverage, regardless of their payer, as CMS' coverage decision process unfolds. The vast majority of rare diseases have no available treatment beyond off-label use of therapies approved for other conditions. Broad use of the national coverage process to drive coverage for Part B drugs will all

but certainly disrupt access to treatments that Medicare's most vulnerable patients rely upon to reduce the burden of their rare disease. In addition, drug development for extremely rare diseases frequently relies on FDA's accelerated approval mechanism, and treatments achieving approval are more costly than drugs for common conditions. Both of these factors have increased the likelihood that a National Coverage Analysis will be initiated and that CMS will seek to implement limited coverage under CED.

AHRQ 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." It further noted that "CMS is confident that the CED NCD process is sound." There is considerable tension between this access-enabling view of CED and AHRQ's goal that its recommended requirements "will 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." One view prioritizes access to promising treatments; the other focuses on Medicare's pool of aged and disabled research subjects. While AHRQ's recommendations on a uniform set of clinical study requirements likely furthers CMS' interest in generating scientifically valid data, they do not address the inherent ethical, logistic, and health equity concerns that CED injects when applied to FDA-approved treatments.

Haystack Project understands the potential that a technology for which a National Coverage Decision is requested may not be supported by a sufficiently robust body of evidence to gain national coverage. Although we agree that CMS likely receives requests that it initiate an NCD for devices, procedures, and laboratory-developed tests, the limited set of CED NCDs (proposed and implemented) for FDA-approved drugs have been CMS-initiated. Haystack is concerned that when CED is directed at FDA-approved drugs, it becomes 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 patients' control (clinical trial availability, eligibility, and randomization) and their willingness to place their care into the hands of researchers rather than the clinicians managing their condition(s).

AHRQ's statutory role in Coverage with Evidence Development (CED) extends to <u>when</u> CED is an appropriate coverage mechanism. The Agency should prioritize ethical research, patient protections, equitable access, and meaningful informed consent.

The Draft Report responds to CMS' relatively narrow request for AHRQ recommendations on CED study design requirements. Haystack Project has significant concerns about the use of CED that are firmly within AHRQ's mission and statutory authority under the Social Security Act. 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 give CMS broad authority to leverage the NCD process as a substitute for AHRQ-determined research priorities.

We urge 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. Specifically, we ask that AHRQ decline to support CED mechanisms or clinical studies associated with safe and effective treatments and/or their medically accepted uses. 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, randomized clinical trials

- Introduces logistic impediments that deny patient access to treatments that are medically necessary for their condition.

CED should not substitute 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

Haystack Project understands that CMS seeks to protect the health and wellbeing of Medicare beneficiaries and ensure the long-term fiscal integrity of the Medicare program. Both CMS and AHRQ cite the inherent uncertainties associated with products that utilize the accelerated approval process. Accelerated approval was devised to prioritize access to promising therapies over scientific certainty. FDA's authority to balance risks and benefits of treatments based on surrogate endpoints within the statutory accelerated approval process is all but certain to result in treatment approvals based on evidence that cannot satisfy CMS' highest bar, i.e., the certainty required to convey national coverage. CMS must, therefore, decide to either:

- Decline to initiate the NCA process for accelerated approval therapies until confirmatory trials are completed (or fail to move forward within a reasonable time) and/or real-world evidence is sufficient to evaluate clinical benefit; or

- Accept that each new accelerated-approval treatment will, despite addressing an unmet need in a serious or life-threatening disease, fail to clear the evidentiary hurdles within the NCA process and access will be foreclosed for every Medicare beneficiary unable to enroll in a clinical trial or absorb the financial cost of treatment.

Individuals with rare diseases and rare cancers disproportionately rely on treatments that would not have been available without the accelerated approval mechanism and will be disproportionately harmed by CED requirements directed at these therapies. CMS can, in theory, single out any, or even all, accelerated-approval treatments, subject them to the critical lens of an NCA, predictably decline access as "national coverage," and offer CED to enable a chance at the access its process foreclosed.

We also note that CMS' Alzheimer's Disease NCA introduced a cost component to NCA scrutiny with the statement that "[m]oreover, with limited exceptions, the expenses incurred for items or services must be reasonable and necessary . . ."[1] Haystack Project believes that this is a bad public policy rationale that could disproportionately impact individuals with as those with rare and ultra-rare conditions, including cancers, and deter development of new therapies. The plain language of Section 1862 does not invite a "cost" inquiry – it precludes Medicare payment for the cost of items and services that are not reasonable and necessary.[2]

The assumptions underlying use of CED for treatments utilizing the accelerated approval pathway are antithetical to Congress' goal of facilitating early access to promising treatments and the FDA's statutory and delegated authority to make safety and efficacy determinations based on surrogate endpoints. We agree that CMS has the authority to decide if and when a particular item or service is reasonable and necessary. The use of the NCA process to scrutinize surrogate endpoints and create an artificial need for CED, however, raises significant and separate concerns, including:

- whether denying coverage to on-label use of drugs and biologicals marketed under accelerated approval frustrates Congress' intent in creating that pathway, i.e., to facilitate early access to promising treatments

- whether one HHS agency is empowered to negate, ignore, or reverse HHS determinations made by another HHS agency (e.g., that a surrogate endpoint is indicative of likely clinical benefit) pursuant to direct statutory or delegated authority.

We believe that, as a matter of policy, CMS and AHRQ should align CED requirements with the intent Congress demonstrated in affirming the accelerated approval pathway and decline to engage in a futile NCA inquiry into whether clinical benefit is confirmed.

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[1] Proposed LCA, Section IX. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&ncaid=305&doctype=all&timeframe=30&sortBy=updated&bc=20

[2] Social Security Act, §1862(a)(1)(A) provides, in pertinent part, that "[n]otwithstanding 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)(A) which, except for items and services described in a succeeding subparagraph, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

CMS use of CED is likely to perpetuate and exacerbate health inequities associated with race, ethnicity, and socioeconomic status.

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. The Administration has taken important and unprecedented steps in recognizing that health inequities and disparities are inextricably linked to centuries of systemic racism; there are no easy solutions to "fix" these economic and health care inequities.

Currently, Black patients make up just 5% of clinical trial populations. CMS and AHRQ should not, however, correct exclusion of Black lives in developing treatments by declining or limiting access once these treatments are approved. 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. 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. Use of CED to determine access to treatments that are within the financial reach of some, but not all Medicare beneficiaries will create a two-tiered system of access where economically advantaged patients achieve early access to care based on physician/patient decision making. and patients without financial resources serve as research subjects and have their treatment determined through randomization.

Conditioning coverage for on-label use and medically accepted, off-label use of FDA-approved treatments on participation in CMS-directed, randomized clinical trials raises significant ethical and logistic concerns.

We have serious concerns that any CED NCD for an approved therapy will place CMS' assessment of benefits versus risks above the very personal decisions on use of FDA-approved treatments that should be inherently within the practice of medicine and the patient/physician relationship. In addition, AHRQ's and CMS' granularity on clinical study requirements and the research questions that those studies must resolve ***raise concerns that CMS is, in and of itself,***

conducting research when it initiates, directs, and evaluates CED studies**.** CMS and AHRQ review and approve study protocols, gather and review data on patient outcomes, and assess study results. The requirement that each CED study be reviewed by an Investigational Review Board (IRB) does not sufficiently protect the Medicare beneficiary population. We urge AHRQ to require 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. We believe this is particularly important when the subject intervention is an FDA-approved treatment, and imperative when that treatment addresses a life-limiting, progressive, and potentially fatal condition for which access will be conditioned on study participation. 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, "control" population.

We strongly recommend that AHRQ include CED requirements to protect beneficiaries ***as patients***, including:

- Creating an alternative coverage pathway for Medicare beneficiaries who are unable 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.

- Limiting CED coverage restrictions to "new starts" so that beneficiaries who are receiving the treatment (through previous clinical trial participation, coverage by another payer, or other means) and exhibiting treatment benefits can continue their treatment. Without this mechanism, patients would have to initiate direct appeals of the NCD to continue their treatment.

- Establishing greater granularity on the informed consent process, including, where applicable:
    - 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
    - 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 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 pay for treatment
    - Disclosure of research subject responsibilities, including consent to invasive and non-invasive tests and imaging studies, that are associated with data collection rather than connected to treatment monitoring

- Requiring that CMS implement a monitoring function over all studies to ensure that randomization of research subjects ceases when likely clinical benefit is shown in a manner generally sufficient for claim-specific payment by a Medicare Administrative Contractor (MAC).

Conclusion

Haystack Project appreciates the opportunity to review and respond to the Draft Report. Patients with cancers and rare conditions rely on the hope that research and development efforts will bring treatment innovations that reduce the burden these conditions exact. We believe that AHRQ is well-positioned to prioritize beneficiary access and protections within its CED requirements and urge that it do so. Please contact Haystack Project's policy consultant, Kay Scanlan, at 410-504-2324 with any questions.


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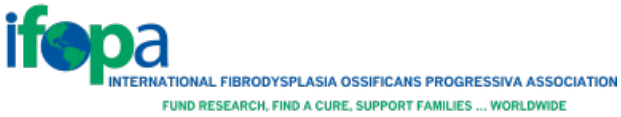
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