



SUBMITTED ELECTRONICALLY

August 21, 2023

RE: (PROPOSED) CMS National Coverage Analysis Evidence Review

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 reviews evidence within the context of 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.

We believe that one of the largest obstacles to improving health outcomes for our patient communities is the risk of unintended consequences due to applying policy priorities and initiatives designed to address the general population without considering the unique challenges associated with rare and ultra-rare conditions. A significant proportion of Haystack Project's advocacy and education efforts focus on identifying and drawing attention to these unintended consequences.

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 could disproportionately harm patients with extremely rare conditions.

A one-size-fits-all approach to evidence review will disadvantage treatments for rare and ultra-rare conditions.

As you know, 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.

Individuals without a disease-specific FDA approved treatment rely on 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 NCAs, can present absolute, impenetrable, and persistent barriers to access if they are implemented without considering the treatment needs of rare disease patients. Any NCA granting coverage for on-label use of an FDA-approved treatment while foreclosing coverage for off-label indications could therefore have an unintended downstream impact on ultra-rare disease patients.

In addition to unintentionally limiting access for off-label use of treatments that might improve outcomes for ultra-rare disease patients, the evidentiary standards set forth in the proposed guidance appear to have been designed to capture "quality" evidence for relatively common conditions. As CMS noted in its proposed guidance, CMS' evidentiary inquiry within an NCA is to "determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary." Haystack Project and the over-130 patient advocacy organizations within its membership are concerned that CMS' stated NCA objective of achieving confidence that "the specific assessment questions raised in an NCA can be answered conclusively" is an insurmountable challenge for new treatments addressing ultra-rare conditions. This is largely due to the fact that research and development on treatments for extremely rare diseases frequently rely on:

- FDA's accelerated approval mechanism
- Use of surrogate endpoints
- Single-arm studies
- Evaluations of treatment impact over a relatively short period of time
- Enrollment of a small set of study participants

The FDA approval processes acknowledge the inappropriateness of a one-size-fits-all approach to evaluating whether the quality and quantity of evidence justifies a determination that a drug is safe and effective. Orphan Drug Act incentives, a dedicated orphan products division for review, the Patient Focused Drug Development Program, and the Rare Disease Endpoint Advancement Pilot Program were initiated to facilitate research and development of rare disease treatments. Haystack Project recently worked with Congress and the FDA on passage of

the HEART Act to address informational and process gaps that have a disproportionate impact on product development in ultra-rare conditions. For example, as most rare diseases do not have a disease-specific treatment, much less a cure, patients are often willing to face a different risk-benefit balance than FDA typically sees. These patient perspectives are not included within clinical trial data but are crucial given that CMS' definition of an intervention that is not reasonable and necessary is one for which the risk of harms outweighs the benefits. The bill encourages FDA consultation with experts in the science of small population studies. This is critical since the small populations for rare and ultra-rare disorders complicate clinical trial design and data analysis by, for example, adding a rescue arm or using historic comparators.

Put simply, the nature of ultra-rare diseases and their patient populations generally forecloses research efforts that would meet CMS' standards of sufficient quality and quantity to justify coverage. Even if CMS would rarely or even never review an FDA-approved treatment that might be used in an ultra-rare condition, the concern that it could do so and would find the evidence insufficient may be enough to deter researchers and their investors.

CMS' Evidentiary Inquiries Should be Driven by Context

The NCA process is an evidence-driven inquiry to determine whether a particular treatment is reasonable and necessary. The level of inquiry should acknowledge and be driven by the evidentiary showing required to obtain market authorization from FDA. For example, coverage decisions involving 510(k) cleared medical devices might afford CMS multiple relevant inquiries, including determining what benefit category the device falls under, and whether the scientific data meets the burden of proof needed to establish that the "reasonable and necessary" standard is met. Drugs and biologicals that FDA approves as safe and effective generally already fall within a benefit category. Although CMS has stated that its medical necessity standard is distinct from FDA's "safe and effective" determination, it has not articulated what, if any, daylight separates a medically accepted use from a reasonable and necessary one. We assume that CMS would require sufficient evidence of patient harm or lack of patient benefit to determine that a safe and effective drug for any medically accepted use was not medically necessary.

Section 1860D-2(e)(4) of the Act defines "medically-accepted" use, in part by reference to section 1927(k)(6) of the Act, to any use of a covered Part D drug which is approved under the Federal Food, Drug, and Cosmetic Act, or the use of which is supported by one or more citations included or approved for inclusion in any of the compendia described in section 1927(g)(1)(B)(i) of the Act. The definition of medically accepted indication also includes drugs used in an anticancer chemotherapeutic regimen for a medically accepted indication by reference to section 1861(t)(2)(B) of the Act. This Part D definition has been applied to Part B drugs within the context of the Medicare Drug Negotiation Program [citation(s)], and we are unaware of any scientific rationale for applying different standards based upon how a treatment is dispensed and administered.

Medicaid programs must justify coverage limitations on medically accepted uses of covered drugs with scientific and clinical evidence. Part D plans and Medicare Advantage organizations must similarly base their utilization management tools and coverage restrictions on evidence, including clinical guidelines. We acknowledge the potential that evidence of harms associated with a drug used for a medically accepted indication may emerge over time and justify CMS' NCA review process. Absent such evidence, however, we urge CMS to decline NCA review of medically accepted uses and to limit any NCA associated with FDA-approved drugs to indications for which there is evidence that harms outweigh benefits. The latter is particularly important for the rare and ultra-rare disease patients still awaiting disease-specific treatments and relying on off-label use to alleviate the disease burden.

Conclusion

Haystack Project appreciates the opportunity to submit feedback on the proposed guidance. If you have any questions, please contact our policy consultant M Kay Scanlan, JD at 410.504.2324.

Sincerely,

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Association for Creatine Deficiencies
Biomarker Collaborative
Casey's Cure Foundation
Choroideremia Research Foundation
CLL Society
CSNK2A1 Foundation
cureCADASIL
Cutaneous Lymphoma Foundation
Dup15q Alliance
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GO2 for Lung Cancer
HealthTree Foundation
Histiocytosis Association
International Cancer Advocacy Network
International Fibrodysplasia Ossificans Progressiva Association
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