March 3, 2023

Submitted to: **mail:** publicinput@pcori.org

RE: Stakeholder Views on Components of 'Patient-Centered Value' in Health and Health Care

Haystack Project appreciates the opportunity to offer its comments on the Patient-Centered Outcomes Research Institute's (PCORI's) draft inventory of attributes of patient-centered value. We support PCORI's efforts to engage with stakeholders across the health care ecosystem and are eager to contribute insights from the patient and caregiver communities living with extremely rare conditions.

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. Haystack Project is committed to educating policymakers and other stakeholders about the unique circumstances our patient communities face, and the important role they collectively play in driving scientific understanding of disease mechanisms, supporting patients and caregivers, partnering with researchers on product development and advocating for fair access to care.

As a threshold matter, we urge PCORI to craft its working definition of patient-centered value to accommodate the unique circumstances and high unmet need in the ultra-rare disease community. Haystack Project's 130+ participating organizations represent patients impacted by a diverse set of extremely rare diseases. While there is commonality among these organizations on their protracted diagnostic journey, paucity of disease-specific experts, and tenuous access to treatment options, there is a great deal of variability on the outcomes and attributes of value they prioritize. PCORI can enhance its potential to improve the real-world experience of ultra-rare disease patients and caregivers by:

- Engaging with the ultra-rare disease patient community by directly funding patient organization-led foundational research projects to aid the patient community's efforts to gain an understanding of disease natural history as well as priority outcomes across patient sub-populations and disease stage. For example, Haystack Project has assisted member organizations in producing "Patient-Oriented Value" reports, but these efforts have been limited by access to funding. Other patient organizations have sought to implement robust patient registries and/or to assess and address inequities and health care disparities among subpopulations within their patient and caregiver communities.
- Including Haystack Project, its patient organizations, and other rare and ultra-rare disease stakeholders in future efforts to define the range of patient-preferred outcomes and assess the personal and economic burden of ultra-rare and rare diseases on patients and caregivers. The

ultra-rare disease patient community did not have robust representation in the extensive set of stakeholders contributing to PCORI's draft report.

- Implementing flexibilities in evaluating research funding requests from the rare and ultra-rare disease communities that do not contemplate a contemporaneous comparator. Small population studies on interventions, including specific treatments or diagnostic tools as well as care delivery innovations, are commonly single-arm studies due to the lack of adequate treatment options. Requirements for active, contemporaneous comparator populations in PCORI-funded studies would preclude most research in ultra-rare diseases.

Our responses to PCORI's specific questions are below:

Q. What patient-centered value attributes are missing from the report?

1. ***PCORI should add several attributes of value for ultra-rare disease patients who prioritize access to the right care regardless of whether there is an FDA-approved treatment or reliance on off-label use.***

In addition to high health care costs, individuals with extremely rare diseases and their caregivers face substantial challenges and significant frustration from symptom emergence through treatment or management of their condition. So several attributes identified in PCORI's draft are particularly relevant to Haystack Project's ultra-rare disease patient community and the overarching priority that patients receive the right care at the right time, including:

- Reduction in uncertainty
- Communication with provider
- Provider competence and awareness of treatment
- Care coordination
- Availability of treatment

However these attributes are elusive within the context of extremely rare diseases. Our patients and caregivers often endure progressive disease symptoms over multiple years before they are diagnosed. It is not unusual for a patient to find that there are just a handful of U.S. clinicians with expertise in managing their specific disease. Many rare conditions impact multiple organ systems, so patients often receive care from multiple specialists, each focused on the organ system within their specialty, and with little or no coordination to address the "whole patient." Therefore, **we ask that PCORI add the following attributes of value:**

- Timely, confirmed diagnosis. For rare and ultra-rare disease patients this might include genetic testing.
- Treatment is guided by a clinician with disease-specific expertise.
- Acute exacerbations are identified and addressed, and potential for subsequent episodes is reduced, if possible.
- Provider respects and "hears" patient. Ultra-rare and rare disease symptoms can be extremely complex, and providers may not recognize that symptoms require investigation and/or referral to specialists for an accurate diagnosis.

- Identifiable "treating physician" coordinating care among specialists and monitoring response to treatment(s).

2. ***Rare and ultra-rare diseases can have a significant impact on patients and their life trajectory. Patients prioritize retaining the ability to live their lives as fully as possible.***

Haystack Project appreciates the robust set of patient-center value attributes identified in PCORI's draft report. However, **we recommend that PCORI include the following attributes:**

- Impact on childbearing potential. Haystack Project has learned from its patient and caregiver community that many "older" treatment options used off-label to address disease symptoms can require delaying childbearing or preclude it altogether. Prioritization of preserving childbearing potential is highly personal and must be assessed within the context of inequities in access to advanced reproductive technologies.
- Participation in educational opportunities. A significant proportion of ultra-rare and rare diseases are genetic with symptoms and progression emerging in childhood. While access to educational opportunities is indirectly captured within the attribute "productivity/ability to work," it also has independent, intrinsic value to patients and caregivers.
- Contribution to Evidence. Patients and caregivers within the ultra-rare disease community struggle daily to fulfill their financial and familial obligations while living with a condition that their friends and families have never heard of or encountered. For many, the "uniqueness" of their journey comes with a strong motivation to ensure that their real-world experience can contribute to scientific understanding of their specific condition and, if research is being conducted, to participate in clinical trials.

Q: What patient-centered value attributes noted in the report do not fully reflect your, or your community's perspective?

Haystack Project appreciates PCORI's effort to obtain granularity on how its identified attributes may have divergent components or importance based on the specific condition and impacted subpopulation. Incentives for innovation, ease of access to care, and the balance between hope and risk among patients with ultra-rare conditions are substantially different from the experience of the general patient population.

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 extremely rare conditions also tend to be costly. Most individuals living with a very rare condition rely on off-label treatments to reduce disease burden and/or slow disease progression.

Haystack Project's rare disease communities struggle to navigate health system challenges in disease states where unmet need is high, and treatment delays and inadequacies can be catastrophic. In addition to the extraordinarily long time from symptom onset to diagnosis, our patient populations and their providers often face a labyrinth of claim denials, prior authorization requirements, reconsiderations, and appeals to access the care they need. Individually, these access challenges can present inconveniences, frustration, and delays in receiving care. Cumulatively, they can present an overwhelming burden for patients and their families.

Below are the attributes on which greater granularity on relevance to the ultra-rare disease community would be important in capturing patient-centered value:

Reduction in Uncertainty and Value of Hope. The ultra-rare disease community views certainty in diagnosis as an extremely high priority. When applied to treatment options, however, there is a significant level of variability in how patients balance uncertainty with hope. Patients generally seek early access to new treatments for ultra-rare conditions that are progressive, life-limiting, and/or life-threatening even when long-term clinical benefit has not been confirmed. Ultra-rare patients live with uncertainty on their disease progression, adequacy of off-label treatments in managing disease burden, and what the future will bring. A new FDA-approved treatment, therefore, likely offers hope that significantly outweighs uncertainty.

Support Network. The concept of "support network" in the ultra-rare disease community emphasizes the importance of patient advocacy organizations capable of connecting patients and caregivers with others living with their condition. These organizations are an important resource in collecting natural history data, connecting patients with providers and clinical studies, and providing patients and caregivers with a forum for sharing information and receiving the emotional support they need.

Quality/Consistency of Evidence. As noted above, clinical studies evaluating treatments for ultra-rare conditions face substantial challenges, including lack of robust natural history data and limited treatment alternatives. Evidence-based medicine approaches to "grading" evidence will almost certainly find that studies sufficient to achieve FDA approval are unreliable or insufficient. Haystack Project expects that it would be virtually impossible to generate high-quality, consistent evidence to support use of a new ultra-rare disease treatment, and sponsor efforts to gather that evidence would delay access for patients with high unmet needs.

Medical necessity. The payer perspective on medical necessity is generally formulaic, relying on private drug compendia listings of specific treatments and their use in specific conditions/populations. Off-label use in ultra-rare conditions, unfortunately, are rarely incorporated into the resources payers use to determine whether a patient can receive a treatment. Treatment regimens developed by recognized disease-specific experts are often the standard of care, but they may fail to clear the "medical necessity" bar payers have developed for more common conditions.

Provider/Health System Impacts (provider experience). Providers treating ultra-rare patients encounter extraordinary administrative burdens in the form of prior authorization, documentation requirements, reconsideration and appeal of denials, and referral to patient assistance organizations. The time and

effort required to ensure that patients are diagnosed and appropriately treated is not reimbursed and may be outside the capacity of community providers.

Financial Impacts/Barriers. Ultra-rare diseases are costly to the patient, their family, and the health system. To the extent that societal costs (i.e., cost of care to payers) are an attribute, they are not patient-centered. For patients, out-of-pocket costs are determined by insurers and their evaluation and/or formulary placement decisions; out-of-pocket costs are not, therefore, inherent to the particular intervention.

Q. What attributes captured in the report do you strongly believe are not a part of patient-centered value?

Haystack Project understands that "disability-adjusted life year" (DALY) is a time-based measure for assessing overall disease burden. DALYs for a disease or health condition are the sum of the years of life lost to due to premature mortality (YLLs) and years of life lost due to time lived in states of less than full health, or years of healthy life lost due to disability (YLDs). **We strongly oppose use of this metric to evaluate the "value" of a treatment or other healthcare intervention in rare and ultra-rare diseases**. Individuals with progressive rare and ultra-rare conditions value each increment of functionality high, and prioritize treatment advances that preserve function – even if that level of function would be considered as below full-health or even as "disabled." Applying DALY would value each year of life as lower in a person with a disabling condition than in a theoretical "full health" individual. The ultra-rare patient community generally views treatments that halt or slow disease progression as miracles; the DALY calculation would likely result in a low assessed value.

Add patient sign ons here.


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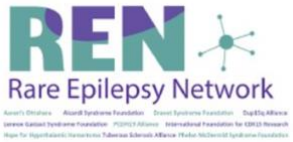
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