



September 25, 2017

Institute for Clinical and Economic Review
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Submitted Electronically: publiccomments@icer-review.org

RE: Proposed Adaptation of the ICER Value Framework for the Assessment of Treatments for Ultra-Rare Conditions

Dear Dr. Pearson,

Over the past several years, increasing attention has been drawn to orphan drugs and their associated costs, with particular focus on the potential for manufacturers to navigate orphan pathways to “blockbuster” sales and revenue. The undersigned* represent diverse stakeholders, including life sciences companies and patient advocacy organizations with a shared commitment to developing and ensuring access to treatments for the subset of rare disorders that impact extremely small patient populations. Our concern that reactive health policies designed to combat perceived orphan drug “gaming” would have an unintended and disproportionate impact on ultra-rare diseases was one of the driving forces toward our collective voice. We believe that ICER’s initiative will have a bottom-line impact on whether or not some patients with ultra-rare diseases will have access to a treatment option.

ICER’s decision to draft an adapted framework for evaluating treatments for ultra-rare conditions was a well-intentioned demonstration of its recognition that there are unique concerns and challenges in developing treatments for extremely small populations. We appreciate the opportunity to offer our comments to ICER’s proposed framework adaptation. We provide a brief introductory summary of the ultra-rare disease stakeholder perspective on the challenges patients, caregivers, and innovators face. Our comments reflect our overriding commitment to preserve, and build upon, the innovation-driving environment envisioned when President Reagan signed the Orphan Drug Act of 1983 (ODA), and are grouped to express our concerns with:

- The foundational assumptions and policy goals driving ICER’s framework;
- ICER’s criteria for determining whether a treatment for an ultra-rare condition should be evaluated within the adapted framework; and
- The potential inappropriateness (and inherent associated difficulties) with making a value judgment intended to drive decisions to grant or deny access to the only FDA-approved treatment for a serious, ultra-rare condition.

We also make specific recommendations to guide ICER's framework and patient engagement strategy in instances, such as diseases with multiple, comparable FDA-approved therapies, where a value assessment for an ultra-rare disease treatment may be of value:

- ICER should incorporate long-term patient benefit into its assessment to accurately capture the value to patients and their families;
- ICER's grafting of Quality Adjusted Life Year (QALY) metrics and a willingness to pay threshold onto evaluations of ultra-rare disease treatments will complicate research and development, and encourage payer denial of necessary medical care;
- ICER should proactively and exponentially increase its engagement with the patient and caregiver community throughout its process; and
- ICER should not directly or implicitly require innovators to provide it with information that is not otherwise publicly available, and not relevant to safety or efficacy.

Background

Congress drafted the Orphan Drug Act's (ODA's) incentive framework to counter the commercial realities associated with research and development toward treatments for serious medical conditions affecting small populations. During the ten years preceding the ODA, just 10 rare disease products had obtained FDA approval; since the ODA's implementation, over 600 rare disease drugs and biologics have been developed. Countless lives have been improved, or saved by new therapies spurred by the ODA, however, millions of Americans affected by a rare disease are still waiting and hoping for treatment or a cure:

- 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 50% of the people affected by rare diseases are children;
- 30% of children affected by a rare disease will not live to see their 5th birthday; and
- Approximately half of identified rare diseases do not have a disease-specific advocacy network or organization supporting research and development.

While the ODA clearly boosted interest in pursuing rare disease treatments, its incentives are a fixed set of counterbalances to the economic calculation of research and development costs, projected risk, and population-based revenue estimates. Reimbursement mechanisms and hurdles can tip the scales for or against pursuing a specific drug candidate for an orphan indication. For patient populations approaching the 200,000 orphan disease limit, the ODA incentives may be sufficiently robust to mitigate clinical trial and reimbursement risks. As affected populations dwindle below 20,000 or even into and below the hundreds, however, the balance is far more fragile.

We support and expect to participate in continuing dialogue among all stakeholders to expand equitable access to quality health care. We are, however, concerned that ICER's efforts to recognize the unique challenges associated with ultra-rare diseases may function only to impede access and inject sufficient uncertainty to chill future innovation. This concern is grounded in evidence -- researchers observe that price thresholds would slow drug innovation by 23-32 percent with as much as a 60 percent reduction in Research and Development (R&D) early stage projects.¹²

Foundational assumptions and policy goals driving ICER's framework

In its concluding paragraphs to the proposed framework adaptation, ICER discussed its guiding principle of attempting to balance competing ethical interpretations of "fairness" in the context of healthcare spending on costly treatments for ultra-rare conditions. Noting the ethics driving reimbursement for high-cost ultra-rare conditions, ICER opined that the balance was well-captured by *Hughes, et al.*, -- "[t]he consequence, however, is that the opportunity cost of supporting the use of ultra-orphan drugs necessitates that patients with a more common disease, for which a cost-effective treatment is available, are denied treatment."³

The undersigned stakeholders include patients with serious ultra-rare disorders, their caregivers, and those who have experienced the life-changing loss of a loved one to a disease for which no treatment exists. Industry signers know what it means to look into the eyes of a parent with the shared hope that a new technology might offer a step closer to a long and fulfilling life for their child. Hughes' world-view, if operationalized and implemented to drive treatment and reimbursement decisions, paints a dark future for individuals with ultra-rare diseases and their families.

A recent study examining the relationship between disease rarity and treatment cost found, not surprisingly, that the cost of orphan drugs in European markets is inversely proportional to disease prevalence.⁴ If it were true that one person accessing their only available treatment might decrease access to several patients with more common conditions (and we do not believe this is an established fact), the "fairness" calculus would always deny treatment to the patient with the ultra-rare disorder simply by virtue of utilitarian principles.

We also note that ICER declined to develop a framework for ultra-rare disease treatments that would have a distinctly appropriate structure and evidentiary standard, stating that "[i]nstead, the goal is that ICER reports be able to provide specific context and additional information so that

¹Vernon A, "Examining the link between price regulation and pharmaceutical R&D investment ." *Health Economics*. 2005. 14: 1-16.

² Kutyavina M. "The effect of price control threats on pharmaceutical R&D investments." (2010).

³ Hughes DA, Tunnage B, Yeo ST. Drugs for exceptionally rare diseases: do they deserve special status for funding? *QJM : monthly journal of the Association of Physicians*. 2005;98(11):829-836.

⁴ Do payers value rarity? An analysis of the relationship between disease rarity and orphan drug prices in Europe, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5405566/pdf/zjma-5-1299665.pdf>

decision-makers will be adequately informed of the distinctive character of the evidence and the broader considerations **that should be part of policy decisions** regarding treatments for rare conditions." (emphasis added) ICER's framework of willingness to pay thresholds and panel votes to categorize treatments as low, medium or high value in monetary terms is in diametric opposition to the "policy decisions" that have already been enacted into law for Medicare, Medicaid, and Affordable Care Act issuers, as well as the contractual arrangements between parties to employer-sponsored healthcare coverage. The US healthcare system is based on the concept that an insured individual is covered for medically-necessary treatments whether their disease is common and its treatment cost low, or their disease is extremely rare with one, costly, available treatment.

Rather than applying the concept of vertical equity in healthcare to assessing value of ultra-rare disease treatments, we urge ICER to follow the lead of clinical and health economic experts such as those convened in conjunction with the Annual European ISPOR Congress in Berlin, Germany, in November 2012. In discussing whether and how to quantify the relative cost and "value" of ultra-rare disease treatments, the expert consensus statement noted:

As to the health economic evaluation of interventions for URDs, the currently prevailing logic of cost-effectiveness (using benchmarks for the maximum allowable incremental cost per quality-adjusted life year gained) was considered deficient as it does not capture well-established social preferences regarding health care resource allocation.⁵

A published cost-effectiveness assessment for enzyme replacement therapy for Gaucher's disease grappled with the inherent tension of monetizing the relative value of a life-saving therapy for an ultra-rare disease. The authors questioned the utility of their inquiry into the incremental cost effectiveness of ERT:

It is highly improbable that, whatever the findings of such research, the ICER could be brought down by the orders of magnitude required to make ERT an efficient use of health service resources. (The possible exception to this would be investigating the most efficient alternative treatment strategies for using ERT in a paediatric population only.) Moreover, if under equity considerations for orphan diseases the NHS feels it is important to provide this drug, regardless of its cost-effectiveness, then refining the precision of the ICER estimate also becomes superfluous.⁶

As more fully detailed below, we ask that ICER refrain from normalizing any cost-based denial of healthcare to these vulnerable patients under the guise of evidence-based, objective, or rational allocation of finite resources.

⁵ Schlander, et al., *Determining the value of medical technologies to treat ultra-rare disorders: a consensus statement*, J Mark Access Health Policy, 2016 Oct 27;4.

⁶ Connock, et al., *The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review*, Health Technol Assess. 2006 Jul;10(24):iii-iv, ix-136.

ICER's criteria for determining whether a treatment for an ultra-rare condition should be evaluated within the adapted framework

To “qualify” for a distinctive assessment approach, ICER proposes that a treatment must be expected to affect a patient population of fewer than 10,000 individuals, with little chance of future expansion of indication or population to above 20K, and it must offer a major gain in quality and/or length of life for patients with a serious condition. ICER opined that:

Only when patient populations near a smaller size of approximately 10,000 individuals does it seem that assessment methods might need to change in some way to recognize the distinctive practical challenges to evidence generation, and to give special consideration to value in the context of the price X volume needed to provide adequate rewards for risk and innovation.⁷

ICER's conclusion that “only” patient populations below 10,000 warrant special consideration provides no context or basis.

- We recommend ICER raise the threshold and explain the basis of its patient-threshold determination. The inverse relationship between disease prevalence and treatment cost supports a more fluid approach;
- The idea that treatments for ultra-rare diseases with near-term (or even concurrent) market potential for non-orphan populations are different from pure ultra-orphan products has some validity. Operationalizing the concept to an assessment that a product has “little chance of expansion” appears to create uncertainty and inject a subjective and speculative component. For example:
 - Is there a presumption of broader utility that must be negated?
 - How “little chance of expansion” determined? Clinical trials in progress? Emerging off-label use? Or is it a more tangential determination relying on shared disease processes and/or scientific speculation?

We urge ICER to keep its inquiry in the near-term, and adhere to its evidentiary standards in assessing “future expansion” rather than engage in speculation. We also disagree with ICER's assessment that potential future expansion beyond 20,000 patients places a treatment in the same category as a potential blockbuster. It is quite possible that a treatment option developed for one ultra-rare condition could be effective for other ultra-rare or orphan conditions. Follow-on indications require innovator investment, could take years to gain approval, and may not come to fruition at all. Moreover, the possibility that a treatment developed for an ultra-rare disease

⁷ https://icer-review.org/wp-content/uploads/2017/05/ICER_Proposed_VAF_Adaptations_Orphan_Drugs_072517.pdf, at p. 3 of 9.

could eventually be more broadly used to enhance the lives of a broader population does not undercut its value – it underscores the potential public benefit of scientific inquiry.

Potential inappropriateness, and inherent associated difficulties, with making a value judgment intended to drive decisions to grant or deny access to the only FDA-approved treatment for a serious, ultra-rare condition

As detailed more fully above, we are concerned that any value assessment of a treatment for an ultra-rare disorder for which no FDA-approved treatment alternative exists would be of limited use to payers due to statutory and/or contractual limitations. We also note that ICER identified a number of instances in which it would be unable to apply its framework. The majority of treatments representing the only available option for an ultra-rare disease would likely fall within these circumstances.

First, ICER notes that when it “judges that it is not feasible to translate measures of patient outcome into QALYs, ICER will provide analyses of the potential costs and consequences of treatment, and will not produce a value-based price benchmark.” Instead, ICER will provide a crosswalk to a treatment and condition pair that is the closest clinical analogue that ICER can identify.⁸ We are unable to envision any situation under which a treatment for a previously untreatable ultra-rare condition should be judged based upon “the closest” surrogate disease state and treatment, and suggest that ICER simply refrain from conducting an assessment that it cannot complete with scientific credibility.

Similarly, ICER notes that “other methodological changes will be made when special circumstances make it extremely difficult to estimate the impact of treatment on quality-adjusted life years, such as when diseases affect very young children or are associated with pronounced mental and/or physical disability in patients of any age.” We agree with ICER that such situations likely will exist, and may even predominate, and appreciate its recognition that the QALY methodology is a poor fit.

Although ICER has suggested that in situations where no treatment has been available in the past, it will seek input from patients and clinical experts on the potential impact of a new treatment on the entire “infrastructure” of care, we do not believe this type of “sidebar” consideration cures ICER’s inability to apply its standards and arrive at fair, ethical, and reasonable conclusions. An assessment purporting to be evidence-based that requires *ad hoc* methodological changes, relies on surrogate disease states, and/or contains disclaimers related to various unmeasured patient and societal considerations strays far beyond the purpose and scope of ICER’s core functions in the overall healthcare system. Again, we urge ICER to maintain

⁸ https://icer-review.org/wp-content/uploads/2017/05/ICER_Proposed_VAF_Adaptations_Orphan_Drugs_072517.pdf, at p. 5 of 9

transparency and scientific integrity, and expend its resources where they can be of greatest value, i.e., in determining the value of a treatment within a subset of available options.

Specific recommendations to guide ICER’s framework and patient engagement strategy in instances where a value assessment for an ultra-rare disease treatment is potentially appropriate

We agree that the challenges to developing and marketing products for ultra-rare diseases warrant a different approach to assessing value than treatments for commonly-occurring disease states. Where providers, patients, and payers have a set of treatment options approved for a specific condition, ICER can play an important role in informing decisions. We are, however, concerned that ICER’s proposed changes and adaptations to address ultra-rare diseases are unlikely to result in meaningful differences in ICER’s assessment or how its assessments are interpreted.

ICER should incorporate long-term patient benefit into its assessment to accurately capture the value to patients and their families.

ICER proposes to retain its generally-applicable standard of evidence when assessing ultra-orphan products, even as it acknowledges that low patient populations may make traditional RCTs impracticable and statistical analyses complicated. A “uniform” approach, particularly one that is substantially the same as the approach used for treatments in large patient populations, will most likely fail to yield meaningful information on specific ultra-rare disease treatment. It will, however, inject additional risk and uncertainty to innovators considering the fiscal prudence of investing in ultra-rare disease therapies.

This is particularly true if the long-term benefits are not sufficiently captured to offset budget impact and provide a more accurate, holistic picture. In evaluating alternative treatment options for ultra-rare disorders, we urge ICER to acknowledge through its value assessment process that the measure of value to patients inherently extends beyond the short-term perspective that payers often adopt. This is particularly true for ultra-rare disorders, most of which are genetic and chronic. Emphasizing the short-term budget impact of treatments using assumptions and arbitrary thresholds may be used as a rationale to restrict patient access.

ICER’s grafting of Quality Adjusted Life Year (QALY) metrics and a willingness to pay threshold onto evaluations of ultra-rare disease treatments will complicate research and development, and encourage payer denial of necessary medical care.

ICER continues to rely on Quality Adjusted Life Year (QALY) as its value metric, just as with all the other treatments (including blockbuster treatments) it reviews. QALY’s suffer significant shortfalls if applied to orphan disease including (1) inability to address the heterogeneity in treatment options; (2) limitations in very young or very old populations; and (3) Caregiver QoL/QALYs usually are not considered despite the particularly profound caregiver in the context of ultra-rare disorders.

A comprehensive study on the use of incremental cost per QALY gained in ultra-rare disorder by Schlander et al., discussed that a growing body of literature considers cost per QALY economic evaluations in ultra-rare diseases as flawed, and likely to set inequitable benchmarks that treatments for ultra-rare diseases cannot meet. Similarly, we are concerned that the willingness to pay framework will serve to impede or delay access to needed treatments. Experience in countries with technology assessment approaches that use rigid willingness to pay criteria experience less and delayed access to treatment options, and lower associated survival rates.

ICER should proactively and exponentially increase its current engagement with the patient and caregiver community throughout its process.

We urge ICER to place patient and caregiver engagement at the center of its assessments. Whether in the context of QALYs or other measures, ICER should aim to gain a better understanding of the outcomes that are relevant and meaningful to patients. In addition, meaningful endpoints specific to patients and their disease state, such as alleviation of symptoms or the ability to be productive in work or home settings, may not be reflected by global or specific clinical measures that feed into a QALY – this reduces the validity of the framework in assessing value on patient-centric outcomes.

ICER discusses outreach to patients and patient groups as part of its inquiry. Unfortunately, this outreach does not start until the process is well underway, with ICER drafting a scoping document and permitting a 3-week time period for public comments. Patient and caregiver stakeholders should be brought into the process to inform the scoping document and identify outcomes that are of substantial importance. Similarly, the 3-week time allotment to become aware of ICER’s activity, review and digest its potential impact, and organize toward meaningful comments and a continuing dialogue is far too short if ICER hopes to have patient perspectives inform the resulting analysis.

We also encourage ICER to maintain transparency with respect to its incorporation of stakeholder input. At a minimum, we urge ICER to ensure that as part of each assessment, it describe how patient input and preferences were considered and incorporated. This will help facilitate accountability between ICER and the patients who will be impacted by its activities, particularly if ICER makes its rationale publicly available. Understanding why certain patient considerations were included and others were not will greatly further the collaborative design ICER seeks to encourage.

ICER should not directly or implicitly require innovators to provide it with information that is not otherwise publicly available, and not relevant to safety or efficacy.

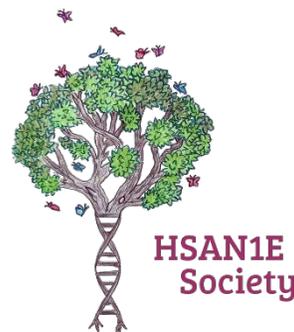
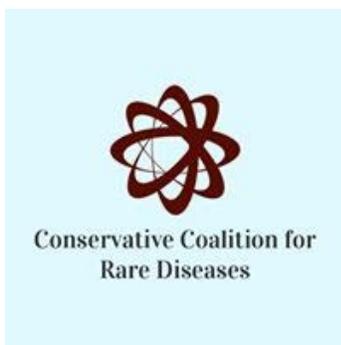
ICER discusses its interest in collecting information on manufacturer development costs, including how it might develop a template. “ICER will work with individual manufacturers of treatments under review to determine what, if any, information related to the costs of development can be shared as part of the public deliberation regarding the value of these treatments and their appropriate pricing.” We are concerned that this level of inquiry is outside the scope of industry standards for manufacturers providing information to FDA, CMS, and

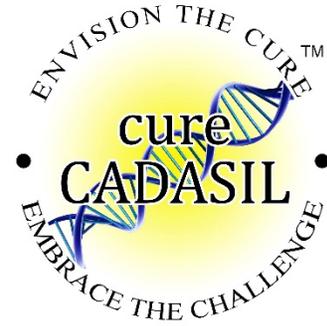
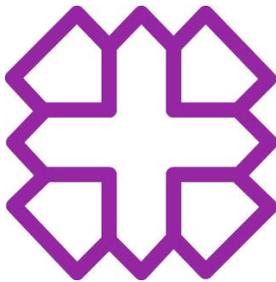
private payers, and may be an unprecedented “reach” by a private entity, particularly considering ICER’s implied goal of broad public disclosure. Our concerns include:

- Intellectual property issues and considerations severely compromise the ability and/or advisability of making these disclosures;
- It is unreasonable for ICER to implement value assessment methodologies that seek or demand confidential industry information;
- Standardizing this inquiry or information request sets up the possibility that ICER would incorporate an adverse inference or otherwise “penalize” rare disease treatments if manufacturers do not cooperate with ICER’s disclosure requests.

We urge ICER to eliminate the disclosure proposal and template development from any final framework it develops.

Once again, we appreciate the opportunity to comment on the proposed framework adaptation. As the voice of ultra-rare disease stakeholders, we look forward to working with you in the future to facilitate patient and caregiver engagement, and to further inform your ultra-rare disease policies, proposals, and frameworks. If you have any questions or would like to discuss our comments and recommendations, please contact Saira Sultan at 202-360-9985.





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**The Haystack Project is an unincorporated association of innovators, patients and caregivers committed to educate and advocate for reimbursement policies that recognize the unique circumstances of extremely rare conditions and treatments.*

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