Biotechnology Innovation Organization

September 25, 2017

BY ELECTRONIC DELIVERY

Steven D. Pearson, M.D., M.Sc., FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: ICER's Proposed Revisions to its Value Framework for Treatments for Ultra-Rare Diseases

Dear Dr. Pearson:

We are writing on behalf of the Biotechnology Innovation Organization (BIO) to provide comments on the Institute for Clinical and Economic Review's (ICER) "Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions" (modified Framework).[1] BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology companies, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place. In that way, our members' novel therapeutics, vaccines, and diagnostics not only have improved health outcomes, but have also reduced healthcare expenditures due to fewer physician office visits, hospitalizations, and surgical interventions.

BIO appreciates the opportunity to comment on these proposed revisions. Patients living with rare diseases often experience significant unmet medical need due to the lack of knowledge about how these diseases are caused or inherited and their progression. That those suffering from rare diseases are predominately children raises issues around how society prioritizes and develops treatments for these conditions. We believe there are significant challenges in reconciling existing population-level value assessment methodologies with the varied healthcare contexts and deeply personal patient-level treatment decisions faced by patients afflicted with rare diseases, their families, and their clinicians. For a number of reasons, applying a patient-centric lens when considering the value of treatment is especially important when considering rare diseases:

[1] July 25, 2017. Available at: https://icer-review.org/wp-content/uploads/2017/05/ICER_Proposed_VAF_Adaptations_Orphan_Drugs_072517.pdf

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- The health consequences of rare diseases can often be debilitating or deadly;

- The manifestation of the burden for a given disease is often unique to individual patients and their caregivers; and

- The healthcare needs of patients with rare diseases are underrepresented in healthcare policy discussions and treatment delivery systems, which are typically focused on broader population healthcare.

Given these factors, we strongly believe that the application of a population-based approach (such as the cost per quality-adjusted life year, or QALY) to value treatment for rare diseases is fundamentally misguided because the assessment principles of population-based approaches inherently under-value the unique considerations appropriate for rare diseases. As such, we believe that a new and innovative approach to value rare diseases should be created; one that focuses wholly on the value of innovation to the individual, their caregivers, and society.

As we noted in our second comment letter on ICER's proposed revisions to its Value Framework earlier this year, we continue to support the assessment of medicines that treat rare and ultra-rare diseases outside of ICER's standard Value Framework. **However, we are concerned that the revisions ICER now proposes would not result in meaningful differences in the way ICER's assessments are presented and interpreted by patients, health plans, consumers, and policy makers.**

Although some of the proposed changes have the potential to capture the nuance and complexity of these conditions, the underlying Framework continues to rely on a methodology that conflates value, short-term affordability, and budget impact. A budget impact threshold has no bearing on clinical decision-making, and as we have commented previously, could mislead those reviewing these assessments into thinking that the arbitrary spending caps put forth by ICER could improve patient care or reduce healthcare costs. In fact, research has shown the negative impact of such caps on patient access to needed medicines, incentives for future innovation, and market efficiency.[2]

We also continue to object strongly to the use of the QALY as the foundational metric of ICER's assessments. Methodological concerns with using QALYs in a decision-making setting are well documented but present unique problems when assessing the value of medicines that treat rare diseases.[3] A QALY distills the entire patient experience for a particular medical intervention into one number. But as the field of personalized medicine advances and interventions can be tailored down to the level of a patient's own genetic code, any rationale for

[2] For example, see Ciarametaro, M., S. Abedi, A. Sohn, C. Fan Ge, N. Odedara, and R. Dubois. 2017. Concerns Around Budget Impact Thresholds: Not All drugs are the same. *Value Health* 20(2):230-233. See also Thomas A. A., and J. A. Wernon. 2007. The cost of US pharmaceutical price regulation: a financial simulation model of R&D decisions. *MDE Managerial and Decision Economics* 28:293-306.

[3] See: Measuring Value in Medicine: Uses and Misuses of the QALY. Partnership to Improve Patient Care. June 2017. Available at: http://www.pipcpatients.org/resources/white-paper-uses-and-misuses-of-the-qaly-ethical-issues-and-alternative-measures-of-value

using QALYs in clinical decision-making fails as a framework. ICER's continued use of the QALY in both its general Value Framework and in its modified Framework for medicines that treat ultra-rare diseases will undermine the goals of personalized medicine.

We encourage ICER and all stakeholders engaged in value assessment to explore less narrow and restrictive approaches to quantifying the value of medicines that accounts for the unique characteristics of the patients and diseases being considered. There is no "one size fits all" definition of value, particularly as it relates to treatments for rare diseases. Value assessment tools that put forward arbitrary constraints as objective fact or employ opaque methodologies harm, rather than aid, the ongoing conversation around value.

In addition to our comments around ICER's approach to value assessment generally, we offer the following recommendations related to the specific changes the Institute is proposing when assessing the value of treatments for ultra-rare diseases.

Sections 1.1 and 1.2 – Criteria and process for use of the modified framework

ICER proposes to "consider" using its modified framework for treatments that are noted as a "potential major advance for a serious ultra-rare condition" when three criteria are met: (1) the treatment envisages a population of fewer than 10,000 individuals, (2) there is little chance of future expansion of indication or population that would extend the size of the treatment population above 20,000 individuals, and (3) the treatment potentially offers a major gain in improved quality of life and/or length of life.

As proposed, we believe these criteria are arbitrary and overly rigid – failing to capture the profound complexity and nuance that exists in the field of rare diseases. Although ICER discusses how other stakeholders both inside and outside of the United States have attempted to define rare and ultra-rare disease, the Institute offers no justification or rationale for why a patient population of 10,000-20,000 should be the range of what is considered "ultra-rare." As no statutory authority or regulatory body in the United States has yet developed a definition of "ultra-rare," **ICER should either defer to using its modified Framework for medicines that meet the statutory definition of "rare disease or condition" as established by the Orphan Drug Act (200,000 individuals in the United States) or abandon strict number limits altogether and instead adopt a more dynamic decision-making process that reflects the complexity of diseases in this space.**

For example, ICER has acknowledged that new treatments will necessarily lead to an increase in disease screening and accelerate diagnoses through greater patient and physician education. It is difficult to know with a great degree of certainty beforehand how much this interaction will change the patient population for a given medicine, making strict numerical constraints on how much the intended patient population can grow while still being considered "ultra-rare" inappropriately limiting.

Flexibility in defining ultra-rare diseases is needed not just because of issues of disease prevalence, but also disease heterogeneity and complexity. ICER's initial ceiling of 10,000 patients in the United States is far too low when considering many rare diseases can be caused by

one of a number of different genetic mutations. Together, the population of patients with a particular condition may exceed 10,000 individuals based on sub-categories within a disease state – thus falling outside of ICER's proposed definition of an ultra-rare disease. However, within that group the mechanism causing the underlying condition may vary greatly, with each requiring a different therapeutic approach.

In deciding whether or not to apply this modified framework to a particular intervention, we also believe the proposed language is ambiguous – illustrating how ICER's current approach to value assessment does not fully account for the range of value propositions for a given medicine. ICER says it will "consider" using a revised framework when its three criteria are met. This implies that ICER could, at its discretion, elect not to utilize the modified framework even when its three criteria are met. Section 1.1 also notes that treatments will be evaluated using these criteria when the treatment presents a "potential major advance." This phrase is highly subjective. Patients, clinicians, payers, and the public may all have differing opinions about what constitutes a "potential major advance" in a particular disease area. Holistic value assessments should not disregard one stakeholder's concept of value in favor of another's. We recommend ICER develop and publish clear criteria around the characteristics that a treatment would have to meet in order to be considered a "potential major advance" in a given therapeutic area. At a bare minimum, ICER should be upfront and transparent about the specific methodologies used to decide when a treatment may offer a potentially major advance.

BIO agrees that treatments for ultra-rare diseases with near-term market potential in non-orphan populations are different from pure ultra-orphan products. We have grave concerns, however, with ICER's broad "solution" of an ICER determination that a product has "little chance of expansion" as it creates uncertainty and injects far too much speculation. **ICER should not conduct assessments, through the modified Framework or otherwise, for treatments addressing ultra-rare conditions for which no alternative FDA-approved treatment exists, unless the manufacturer or patient groups request an assessment in response to access constraints.** This should also apply to situations in which there are symptomatic, but no disease-modifying therapies available on the market.

ICER's stated goal in each of its assessments under the modified Framework is to "provide specific context and additional information so that 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." ICER's framework of willingness-to-pay thresholds and panel votes to categorize treatment value may further its goals where providers, patients, and payers face a decision among treatment options with similar efficacy profiles. However, for patients seeking access to the only FDA-approved or disease-modifying therapy for an ultra-rare disease, the "value" calculation morphs to deciding whether the improved quality and/or duration of their lives is worth the money within an artificial construct in direct conflict with the "policy decisions" that have been codified for Medicare, Medicaid, and commercial issuers. It also would stand in contrast to existing coverage standards under many federal programs that require coverage of therapies that mitigate or halt the

progression of the underlying disease even when therapies that treat only the symptoms of the disease are also available.[4]

We also recommend ICER resolve ambiguity around the terminology it uses when discussing diseases assessed under the modified Framework. In introductory language, the Institute focuses on "rare" conditions and explains why additional methods are required for assessing the value of therapies targeted for rare conditions. In Section 1.1 however, the Institute changes course and asserts that adapted methods are not necessary for the majority of orphan drugs. Elsewhere in the report, ICER appears to use the terms "orphan," "rare," "ultra-rare," and "serious ultra-rare" interchangeably – leading to confusion. ICER should define and use consistent terminology throughout the finalized modified Framework.

Section 2.1 – Standards of evidence

ICER proposes to not change its standards of evidence or Evidence-Based Medicine (EBM) rating matrix when assessing treatments under the modified Framework. It would instead discuss relevant difficulties in generating evidence for treatments with very small patient populations (randomized controlled trial challenges, long-term data on safety, and durability of clinical benefit).

We recommend ICER abandon use of its EBM rating matrix when assessing treatments under the modified Framework. Because ICER will not incorporate functional changes to account for the inherent uncertainty surrounding clinical evidence for treatments with very small patient populations (or for treatments that have not yet been or only recently approved by the FDA), we are concerned that any evidence-rating under the existing EBM would inappropriately find the body of available evidence "inconclusive" – confusing stakeholders about the value of these treatments and potentially limiting patient access. We do not believe that a qualitative discussion of these issues is sufficient to negate any prominent display that, according to the ICER-developed EBM, there is inconclusive evidence for a particular treatment.

Sections 3.1–3.4 – Willingness-to-pay and value-based pricing benchmark adjustments

Standard cost-effectiveness models would be produced for treatments under the modified Framework. However, reports would acknowledge the uncertainty in translating patient outcomes into QALYs for ultra-rare conditions. The proposed revision would widen ICER's willingness-to-pay threshold to $50,000 - $500,000 per QALY, with no special weighting for individual conditions. Value-based price benchmarks would continue to use the standard range of $50,000 - $150,000 per QALY, but the reports will note that stakeholders often give special weighting or other considerations for medicines that treat ultra-rare diseases that lead to higher-

[4] As just one example, under the EPSDT standard, if there are no other services that are comparable in terms of safety and effectiveness, then the service at issue is likely to be found medically necessary, and thus, must be covered for Medicaid-eligible children. See Centers for Medicare & Medicaid Services, EPSDT – A Guide for States: Coverage in the Medicaid Benefit for Children and Adolescents, at 10 (2014), *available at* https://www.medicaid.gov/medicaid/benefits/downloads/epsdt_coverage_guide.pdf.

cost effectiveness ratios. When ICER cannot translate relevant inputs into QALY measurement, it proposes to cross-walk available data to a cost-consequence price.

Notwithstanding our objections to the use of QALYs described above, we support the broadening of the willingness-to-pay threshold. We recommend ICER also expand its value-based pricing benchmark for these treatments to reflect their long-term value.

Traditional incremental cost-effectiveness ratios are inherently higher for treatments that will be administered (or whose benefits accrue) over very long time horizons. Not broadening the value-based pricing benchmark in conjunction with the broadening of the willingness-to-pay threshold for these treatments penalizes medicines that treat or cure diseases that would otherwise impact an individual for his/her entire life.

We believe that ICER should strongly and clearly characterize the inherent uncertainty in developing cost per QALY metrics for ultra-rare diseases. Much smaller patient populations than those for traditional therapies introduce greater variability across a range of metrics. ICER should be prepared to describe in detail how a "high" cost per QALY measurement could be due to the uncertainty in dealing with small populations. We note that many of these considerations also exist when assessing the value of innovative medicines for serious diseases with patient populations greater than 10,000.

We also have numerous concerns about the process by which ICER would conduct its reviews when QALYs cannot be derived from patient outcomes measures. Substituting data from one indication to another – with no apparent checks or independent assessment of their appropriateness as a proxy – risks undermining ICER's fundamental approach to value assessment. These types of substitutions can also suppress the nuance and uniqueness of the patient voice. ICER should avoid creating ad hoc methodologies to make the assessment of a new treatment feasible. **We recommend ICER categorize and prominently note that assessments conducted under this process are "incomplete."**

Section 4.1 – "Other benefits and disadvantages" and "contextual considerations"

Consistent with its recent changes to the standard Value Framework, ICER would work with stakeholders to incorporate "other benefits and disadvantages" and "contextual considerations" into these assessments.

BIO supports the inclusion of a broad range of societal impacts when assessing the value of all medicines – not just those that treat ultra-rare diseases. We encourage ICER to work collaboratively with patients living with these conditions and the clinicians treating them to understand the full range of impacts that treatments for potentially debilitating conditions can bring. As ICER alludes, treatments for ultra-rare diseases require even more context and consideration of societal effects as the treatment being assessed is often times the first in its class.

While we support ICER's proposal to explore and include these factors in its assessment of these treatments, we request the Institute provide additional clarification around how these

benefits will functionally impact ICER's reports. As we commented in the revisions to the standard Value Framework, these factors must not only be investigated and described in the assessment, but meaningfully impact its outputs. Specifically, it is unclear whether ICER will utilize these considerations in its assessment of "value for money." We understand the difficulty in incorporating non-quantifiable or other metrics that fall outside the traditional dimensions of cost-effectiveness analysis. But we encourage ICER to work with stakeholders to the greatest extent possible to ensure these other considerations are incorporated into its assessments and conveyed to stakeholders in a meaningful way.

As part of this engagement, 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's goal should be 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 – effectively reducing the validity of the Framework in assessing value on patient-centric outcomes.

We also encourage ICER to engage patients and caregivers at the start of its process, to inform its initial draft scoping document, and throughout its evidence collection and analysis process. The Institute should 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.

Section 5.1 – Research and development costs for new treatments for ultra-rare conditions

ICER proposes to develop a template for manufacturers to provide information on the "research, development and other relevant costs related to new treatments for serious ultra-rare conditions" that would be included in future ICER reports.

We strongly object to ICER attempting to collect this information from manufacturers and recommend the Institute halt its efforts to develop methods to incorporate it into future reports. As a private third-party entity, ICER does not have the authority to seek or publish this type of competitively sensitive information. The organization also lacks sufficient safeguards to ensure any information given to ICER would remain confidential.

Attempting to collect relevant research and development costs for any one therapy also presents significant operational hurdles that vastly outweigh supposed benefits of its disclosure to ICER. Many manufacturers develop multiple product lines simultaneously, with a discovery in one area informing investment in another. In the pre-clinical phase, a company may make broad-based investments that have significant impact over time but are not linked to any one product in particular. Prices for approved medicines must also account for the research and development of those products that are investigated but ultimately fail. Finally, mergers and acquisitions, licensing, and joint development arrangements would greatly impede the development of any common template that could be used across different products. Isolating the research and

development costs for any one product would therefore be extremely difficult – if not impossible.

Section 6.1 – "Long term value for money" designation

Votes on a medicine's "long-term value for money" would still be conducted under the base case of $50,000 - $175,000 per QALY, but medicines falling above this price threshold would no longer receive a designation of "low" long term value.

BIO agrees that medicines assessed under this modified framework should not be designated as "low value." Rather than operating under the arbitrary constraint of $50,000 - $175,000 when determining long term value for money, we recommend ICER deliberate solely on the contextual consideration and other benefits and disadvantages when assigning this designation, given that there are many other equally valid considerations.

Conclusion

BIO appreciates the opportunity to submit our feedback on ICER's revisions to its Framework for treatments for ultra-rare diseases. We hope this continued dialogue will help to produce tools for value assessment that recognize value's dynamic nature and fully incorporate the nuance and complexity of issues surrounding treatments for rare disease. Please feel free to contact me at (202) 962-9200 if you have any questions about these comments or if we can be of further assistance.

Sincerely,

/s/

Alex Keeton
Director
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