June 10, 2019

Submitted electronically to: publiccomments@icer-review.org

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

Re: Input for ICER's 2020 Value Assessment Framework

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide input as ICER considers improvements to its value assessment framework for 2020.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient access to approved therapies and appropriate clinical care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of physicians promoting the benefits of patient-centric health policies. IfPA is a 501(c)(3) public charity non-profit organization.

Comments Regarding ICER's Value Assessment Framework

ICER's request for input emphasizes four topics, which form the basis of IfPA's comments.

1. **The cost-effectiveness thresholds ICER uses to establish its value-based price benchmarks for treatments of both common and ultra-rare diseases.**

IfPA Recommendation: ICER should adjust its cost-effectiveness thresholds to account for the unique burden of each disease. The rarity of a disease is an important consideration, but it is not the only justification for adjusting the cost-effectiveness threshold. ICER should also adjust the cost-effectiveness threshold to account for other factors – such as impact on co-morbidities or other difficult-to-quantify medical benefits.

ICER is right to adjust its cost-effectiveness thresholds when evaluating therapies for rare diseases. As exemplified by the Orphan Drug Act of 1983, evaluating orphan drugs differently than

treatments for more common diseases can increase the number of therapies that improve or save the lives of people with rare diseases. There is an important parallel between granting longer exclusivity periods to the developers of orphan drugs, as the Orphan Drug Act did, and adjusting ICER's cost-effectiveness thresholds for orphan drugs. In both cases, patients benefit.

Were ICER to apply its standard threshold range when evaluating therapies for rare diseases, the high cost of development coupled with the small patient population could bias ICER's findings against finding the drugs cost effective. But, just as Congress' adjusting exclusivity measures to incentivize orphan drug development resulted in more treatment options for patients, adjusting the cost-effectiveness thresholds for ICER's analyses can result in better treatment availability – by increasing the likelihood that the drugs are found cost effective and provided adequate coverage by health plans.

That begs the question: Shouldn't other patient populations have the benefit of a threshold that specifically addresses the unique burden of their disease? Rarity should not be the only criteria ICER considers when adjusting cost-effectiveness benchmarks. ICER could commonly adjust the threshold ranges to accommodate considerations such as a condition's co-morbidities, a treatment's impact on adherence rates, a condition's impact on patients' quality of life, and the unquantifiable costs and burdens that patients must live with, such as pain. These considerations can vary significantly depending on the condition and treatment.

For one example of why ICER might adjust cost-effectiveness thresholds for other criteria, consider issues that arose when evaluating CGRP inhibitors for migraine patients. Migraine is one of the most prevalent neurological disorders worldwide, associated with substantial health, sociological and economic consequences. One common health comorbidity of chronic migraines is depression. Studies indicate that up to 80 percent of chronic migraine patients exhibit symptoms of depression. Further, depression is associated with worsened migraine-related disability and reduced quality of life. Depression is also an important risk factor for suicide. Due to these considerations, effective migraine relief will meaningfully improve patients' welfare beyond benefits measured in terms of "fewer migraine episodes" or "less severe migraine-related pain."

By adjusting the cost-effectiveness thresholds, ICER could account for these other benefits. And, as with orphan drugs, adjusting the cost-effectiveness threshold range for important considerations, like a condition's co-morbidities, will help ensure that cost-effectiveness evaluations are not biased against certain patient groups.

2. **The approach ICER takes to evaluate the magnitude and certainty of net health benefit demonstrated by the clinical evidence, as well as how real-world evidence can be incorporated into these judgments.**

IfPA Recommendation: ICER should adjust its approach to rely primarily on real-world evidence for evaluations. This would require ICER to time analyses differently, evaluating therapies at a point when sufficient real-world evidence exists. In particular, ICER should ensure that researchers have a sufficient amount of real-world, long-term impact data before they attempt to evaluate a medicine's cost-effectiveness.

Patient access is best served when ICER findings are based on real-world evidence, not just clinical trials data. In fact, the use of clinical trial data exclusively is, by definition, insufficient for evaluating "the magnitude and certainty of net health benefits." As the FDA explains regarding the drug development process:

> Even though clinical trials provide important information on a drug's efficacy and safety, it is impossible to have complete information about the safety of a drug at the time of approval…**.** The true picture of a product's safety actually evolves over the months and even years that make up a product's lifetime in the marketplace.[1]

Despite the need for "months and even years" of data to understand "the true picture" of a drug, ICER will sometimes evaluate the cost effectiveness of drugs that are still in clinical trials. For example, ICER evaluated CGRPs in 2018 while these drugs were still in phase II or phase III clinical trials. The clinical and safety data for these medicines was limited, and the important post-marketing data, which the FDA itself notes is critical, was not yet available.

In another example, when ICER evaluated the benefits of monoclonal antibodies for the treatment of moderate-to-severe asthma, the studies available had not yet reviewed the impact from the medicines on the variables that ICER cited as important for determining value. These included measures such as the number of emergency room visits, the number of hospitalizations, and several quality-of-life indicators typically applied to asthma patients.

These data deficiencies are most troubling with respect to any long-term conclusions that ICER may draw. When ICER evaluates drugs that are still in clinical trials, or have been approved only for a short period of time, there can be no available data on the long-term benefits, long-term safety and long-term adherence rates. This means that ICER must extrapolate the long-term effects of a medicine based on short-term data.

Extrapolation introduces unknown biases into the analysis. In fact, ICER often notes these constraints in its "Limitations" sections. With respect to the CGRP inhibitors, for instance, ICER noted that "the models were based on *clinical trial results that may not hold true for longer time horizons* or in particular patient populations different than those seen in the trials." Noting this limitation does not eliminate the concerns, however. Considering limitations that arise without sufficient real-world data, IfPA urges ICER to consistently include real-world clinical and price data into its cost-effectiveness models.

3. The use of both the QALY and the evLYG to evaluate the degree of improvement in health outcomes.

IfPA Recommendation: ICER should phase out the use of QALYs and evLYG. If these metrics cannot be universally phased out, ICER should at least refrain from using the QALY and evLYG when evaluating treatments for mental health care, treatments for rare diseases, and treatments whose benefits are inherently qualitative.

[1] https://www.fda.gov/patients/drug-development-process/step-5-fda-post-market-drug-safety-monitoring.

IfPA remains concerned that the QALY inaccurately measures how treatments can increase health outcomes, particularly for diseases that are inherently qualitative. The evLYG metric eliminates the "quality" adjustment associated with QALYs but suffers from the same inherent flaw: imposing a precise quantitative estimate that cannot reflect the individualized value a patient places on his or her own health. These metrics suggest that an objective analysis is possible, when in reality the value of the treatment is inherently subjective and varies greatly across patients and disease states.

Should ICER continue to use these metrics, it is imperative to recognize that the flaws inherent in the QALY metric create larger problems for diseases whose afflictions are harder to quantify. How does one assign a value to the embarrassment and stigma of, as with tardive dyskinesia, having one's face contort uncontrollably in public? How does one quantify the discomfort of poorly tolerated treatments for psoriasis, or the pain and daily inconveniences of rheumatoid arthritis? Treatments for some disease states simply do not lend themselves to economic number crunching.

As noted by Hyry et al. (2014), cost-effectiveness assessments are also flawed with respect to rare diseases because the small population size, by definition, raises the costs per patient.[2] This size limitation significantly constrains the applicability of the QALY / evLYG methodology to rare diseases.

Further, as documented in a review of the literature that examined the limitations of the QALY methodology:

> …The QALY system could lead to an innate preference for life saving over life enhancing treatments because preventive or basic long-term care measures generally score lower on QALY calculations than more dramatic treatments. This places certain interventions at a disadvantage – for example those in mental health care, where treatment modalities largely fall into the remit of life enhancing measures.[3]

These considerations demonstrate that the QALY / evLYG methodology underestimates the benefits for patients that are living with many types of diseases. Consequently, if ICER is going to continue to apply the QALY / evLYG methodology, IfPA urges ICER to apply this methodology only to common, life-threatening, diseases where the biases inherent in the QALY / evLYG methodology are least problematic.

4. Methods by which to integrate those potential benefits, contextual considerations, and other factors relevant to judgments of an intervention's value that cannot be easily captured through review of the clinical evidence or through cost-effectiveness modeling.

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[2] Hyry H.I., Stern A.D., Cox T.M., and Roos J.C.P. (2014) "Limits on use of health economic assessments for rare diseases" *QJM: An International Journal of Medicine*, Vol. 107, Issue 3,1, March; https://academic.oup.com/qjmed/article/107/3/241/1570371/Limits-on-use-of-health-economic-assessments-for.

[3] Pettitt DA, Raza S, Naughton B, Roscoe A, Ramakrishnan A, Ali A, Davies B, Dopson S, Hollander G, and Smith JA (2016) "The Limitations of QALY: A Literature Review" *Journal of Stem Cell Research & Therapy*, March 29; https://www.omicsonline.org/open-access/the-limitations-of-qaly-a-literature-review-2157-7633-1000334.php?aid=70859 (emphasis added).

IfPA Recommendation: Accounting for other factors requires a methodology that accommodates two important considerations. First, the methodology should consistently incorporate the quantifiable broader social benefits that the treatments can provide (such as increased worker productivity, decreased social costs, and reduced comorbidity costs). Second, the methodology should not provide a conclusive cost-effectiveness evaluation when there are significant unquantifiable benefits that a treatment can provide (such as a reduction in chronic pain).

Patients do not differentiate between the types of benefits that interventions provide them. These benefits obviously include improved health outcomes, but they also include the reduced costs associated with comorbidities, the reduced burdens on caregivers, the increased ability to earn a living or have their kids attend school, or the reduced social costs that can be associated with some diseases. It is imperative for ICER to incorporate into its cost-effectiveness methodology comprehensive measures of the benefits patients receive from treatments.

ICER's 2017 draft report on abuse-deterrent formulations (ADF) of opioids demonstrates what happens when certain considerations are excluded. The analysis failed to quantify several important benefits that ADFs could provide. Consider ADFs' impact on opioid diversion as an example.

Severtson et al. (2013) found that OxyContin diversion fell 53 percent in the period immediately following the introduction of the ADF version.[4] By five years after the introduction Severtson et al. (2016) found that the reduced diversion rates continued.[5] By reducing diversion, ADFs also reduce the social costs that opioid diversion generates including increased rates of abuse, increased criminal justice costs and decreased worker productivity. ICER's report did not adequately incorporate these savings, which are one of ADFs' foremost potential benefits, significantly understating abuse-deterrent opioids' overall value.

As this example illustrates, the measured benefits from the ICER studies will often be significantly impacted by the non-medical expenditure benefits. From a patient perspective, the benefit from these costs are no less valuable than the medical expenditure benefits received. Thus, the full dollar value of these benefits should be incorporated into ICER's cost-effectiveness modeling.

Cost-effectiveness studies that under-measure these other patient benefits are biased toward a finding of "not cost-effective" when a full accounting of the benefits would demonstrate that patients in fact benefit greatly from the treatment. ICER's cost-effectiveness modeling should always incorporate into its analyses quantitative estimates of the non-medical expenditure benefits and any reduced social costs enabled by the medicines.

It is important to emphasize that, as stated earlier, not all of these "other" benefits will be quantifiable. For those indications where a large number of benefits are not quantifiable, it is important that sufficient caveats regarding the quantified cost-effectiveness measures are provided. These caveats should make it clear that, despite the precision of the cost-effectiveness estimates, there is a large amount of uncertainty regarding the estimate. Further, when this uncertainty is

[4] Severtson SG et al. (2013) "Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010" *Journal of Pain* October 14(10); https://www.ncbi.nlm.nih.gov/pubmed/23816949.
[5] Severtson SG et al. (2016) "Sustained reduction of diversion and abuse after introduction of an abuse deterrent formulation of extended release oxycodone" *Drug, Alcohol Dependency* November 1;168; https://www.ncbi.nlm.nih.gov/pubmed/27716575.

particularly large, it may even be inappropriate to provide a specific cost estimate. Under such conditions, a specific estimate indicates a level of precision that is simply unrealistic given the large number of unquantifiable benefits.

Conclusion

The conclusions from ICER's cost-effectiveness evaluations can impact patients' access to needed treatments. Unwarranted restrictions will negatively impact their quality of life, and for some patients, can mean the difference between life and death. It is imperative, consequently, that ICER's value assessment framework properly incorporates all potential benefits that a treatment can offer patients, including those benefits that are difficult to quantify or are unquantifiable. Ignoring these benefits will bias ICER's results and lead to inappropriate access restrictions for patients.

Just as importantly, ICER should apply its framework flexibly. Disease pathologies differ from one another, as does their impact on patients. There is not one framework that can capture the full costs and benefits associated with treatments for these different diseases; consequently, applying one rigid framework across the many different treatments available for patients will lead to inapplicable conclusions for many disease areas. ICER should account for this reality by adjusting its cost-effectiveness thresholds and whether it will apply the QALY methodology for different treatments.

Thank you for the opportunity to provide comments on these important issues. Please contact IfPA should you have any questions, or would like us to provide further comments, at 202-499-4114.

Sincerely,

Brian Kennedy
Executive Director