

June 10, 2019

BY ELECTRONIC SUBMISSION

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

RE: ICER National Call for Public Input for 2020 Value Assessment Framework

Dear Dr. Pearson,

AESARA respectfully submits our response to the Institute for Clinical and Economic Review (ICER)'s call for public input on how to improve the ICER value assessment framework methods and processes.

AESARA Inc, is a digital-forward market access agency that designs innovative solutions enabling transformative market access. AESARA combines first-hand industry and payer experience with a broad external network and market knowledge. We work with life science companies to strengthen market access strategies, value evidence generation and evidence communication. As trained health economists and outcomes researchers, with direct industry experience, we are well-familiar with both scientific methodologies and standards set for the highest caliber of research. Further, we keenly dedicate our efforts to help ensure the best health care is available for every person who needs it.

AESARA commends ICER for opening the opportunity to inform value assessment approaches to the public. To date, ICER improvements to their methodologies and processes, particularly in the 2017-2019 update to their value framework, have helped ICER adhere more closely to well-established principles and standards for clinical effectiveness and health economic research. AESARA applauds this advancement.

Yet, important limitations persist and AESARA further supports initiatives that effectively and fully align ICER practices to the highest standards established in the scientific research community. Ultimately, the best science is not about science alone; rather the best science is about ensuring the best evidence is available for decision-making. This is no more important than in health care where each decision, at each point through the process, ultimately affects a person's life.

AESARA strongly recommends ICER consider the following as two top priorities in any further initiatives undertaken, to not only improve their methods and processes, but to ensure the

strongest and most accurate information is available to inform decisions directly related to patient access.

Priority 1. Assessments to inform US access and reimbursement must align with the structure, context and practice of the US health care system to be relevant for payer decision-making and patient access to needed health care.

1. While affordability remains a growing concern, the ICER approach of basing policy recommendations on a budget impact analysis conducted at the national level is fundamentally flawed when applied in the US.
 - The current ICER approach adapts that applied in the UK (single payer system) to the US (fragmented system across 900+ payers).
 - Thusly, the ICER national budget impact analysis does not pertain to the current US health care system, payers and patient populations.
 - Further, the approach is influenced by factors not necessarily reflective of the value new medicines provide to patients, which may carry unintended consequences.
 - Whether this ultimately influences access, pricing, or perhaps even the timing of FDA application submissions is yet to be seen; regardless, such approaches and their implications – and limitations – must be made transparent, prominent and clear to all.
2. If ICER cost-effectiveness models will be used to influence real-world pricing of new interventions and access for patients, such models should reflect real-world context and practices.
 - ICER does attempt to develop economic models with the best evidence available and when evidence needed to reflect the real-world is not available, ICER appropriately discloses such and outlines the alternative approach.
 - However, when using results of non-real world models, ICER does not transparently disclose the limitations of such models nor provide guidance in how such results should be considered in the real world.
 - Further, ICER boldly uses the results of non-real world models to set recommendations for pricing and/or access and affordability alerts for real-world practice.
 - The alarming result is that payers using ICER reports without specific health economic modeling expertise may not have the information available to appropriately interpret such non-real world models; in using the results, they may set policies based on misinformation.
 - Further, failure to present results in the appropriate context and with proper guidance for interpretation and real-world application may lead to communications that are not truthful and/or are misleading.

Priority 2. Well-established standards for research, interpretation, and communication exist based on decades of research by the strongest scientists around the world; value assessments should adhere to such standards particularly as the alternative means potentially basing policy for patient access on misinformation.

1. If ICER desires to use cost-effectiveness modeling as a basis for recommendations, established health economic standards should be applied with the use of the totality of evidence generated to understand drivers, variability vs. stability of modeling estimates, and likelihood of cost-effectiveness in applied settings.
 - Although ICER has expanded its use of sensitivity and scenario analyses to better align with established health economic standards, ICER determinations of long-term value based on cost-effectiveness rest on the base case.
 - Results of sensitivity and scenario analyses are rarely presented in the Report-at-a-Glance or other summaries, and recommendations are presented relative to the base case alone; this does not align to the best practices of cost-effectiveness methodologies to appropriately reflect the inherent uncertainty of economic models.
 - Sensitivity and scenario analyses are intended to provide deep insights into the degree of variability and, where uncertainty exists, the extent to which it may impact results; without having these insights, audiences are missing pivotal information to understand the full economic analysis.
 - While uncertainty results may be reported in the ICER Final Report, these are not reported consistently, where some reports include them in the main body and others in the Appendices with varying degrees of detail; this may make it difficult to users to consistently identify all relevant results in the Report.
 - Across all reporting mechanisms, the totality of evidence should be summarized for easy interpretability; the totality of evidence includes not only the base case but also the degree of uncertainty with supporting documentation and rationale.
 - Failure to provide full disclosure as described above indicates poor application of economic methods and opens the potential for misinterpretation and misuse of results and recommendations based on the ICER models.
2. ICERs current approach to value-based pricing assumes cost-effectiveness is the value-determinant for pricing and a threshold can reasonably be used across payers and patient populations; this has not been established in the US.
 - ICER's current approach to use cost-effectiveness thresholds to identify "value-based pricing benchmarks" is a function of various undisclosed and untested assumptions.
 - Value-based pricing is the ideal pinnacle to achieve across the health system, particularly for patients, yet value definitions and quantification will likely vary widely across the US.
 - The critical discussion point is not the cost-effectiveness thresholds ICER uses to establish value-based price benchmarks, as requested for specific input; rather, the

critical discussion points are whether cost-effectiveness can be appropriately used to set such benchmarks for pricing and whether ICER approaches would be robust enough to support such mechanisms.

3. Introduction of a new, untested and unvalidated metric, such as the Equal Value of Life Years Gained (evLYG), does not address the long-going debate on whether the QALY is the best measure for cost-effectiveness, and further complicates the use of economic modeling for decision-making particularly given that there is no evidence to the performance of such a metric.
 - ICER has released limited information on the evLYG beyond a two-page synopsis
 - It remains unclear whether the evLYG may add substantively to the body of evidence that may be generated through ICER cost-effectiveness modeling, particularly as ICER already has significant challenges in applying the body of evidence generated by their models per well-established methods and practices.
 - Consideration of a new metric may be appropriate for pilots, but should be bolstered by the appropriate research led by appropriate experts before such metrics are put into place to influence recommendations and decisions that direct patient access to needed care.
4. Several adjustments should be made in the ICER Reference Case to enable ICER approaches to fully and effectively align to well-established research standards and practices.
 - The reference case notes many of the elemental components of conducting comparative effectiveness analysis and health economic evaluations.
 - However, important information is not captured in the reference case or in ICER documentation, which limits the appropriate interpretation and use of results.
 - Current documentation does not enable even trained health economists to fully understand the reasons for particular inputs, scenario analyses or other factors; non-health economists not only may not know how to interpret results appropriately but even further, may not realize what limitations exist for doing so.
 - Formatting guidelines for the economic assessments may better assure the conduct and reporting of economic analyses is systematic, consistent, more easily understood and more practically referenceable.
 - All ICER documentation (including Draft Reports, Final Reports, Reports-at-a-Glance, and others, where ICER modeling results are disseminated) should summarize and appropriately interpret the totality of evidence versus a single base case.
 - The same standards should be applied to ICERs work as that of scientific researchers when disseminating results at scientific congresses and within peer-reviewed publications and should be considered the minimum for a policy organization serving the US and aiming to appropriately inform recommendations for patient access to needed care.

In addition to the above two top priorities, AESARA would like to briefly note the below as additional important considerations that we believe will strengthen ICERs approach, impact and improve decision-making related to access to intervention for patients. We encourage ICER to:

- Prominently disclose rationales for the selection of specific topics for review, and to also disclose rationales when topics are not selected for review;
- Expand assessments for “ultra-rare” diseases to include “rare” diseases;
- For indirect treatment comparisons, publish the methods employed including search criteria, how studies were assessed, what studies were included with rationale, what studies were excluded per criteria, and the potential impact of excluding such results; this follows similar practices recommended by the FDA under Section 3037, *Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers*;
- Consider expanding assessments to address wider health care system impacts and efficiencies;
- Share ICER economic models fully, with the ability to use the model as well as explore the data informing the model;
- Progress from current reporting ICER model validation to fully pressure-testing the model, particularly given the import of the use of such models for policies that affect patients across the US.

AESARA appreciates this opportunity to participate in the process and discussion of value assessment in the US with ICER. We look forward to reviewing the draft revisions to the ICER value framework in August. Please direct questions to Sissi Pham at sissi@aesara.com.

Sincerely,



Sissi Pham, PharmD
CEO, AESARA, Inc
Sissi@aesara.com

June 10, 2019

BY ELECTRONIC DELIVERY

Institute for Clinical and Economic Review

One State Street, 10th Floor

Boston, MA 02109

publiccomments@icer-review.org

RE: ICER National Call for Proposed Improvements to 2020 Value Assessment Framework

Alnylam Pharmaceuticals, Inc. welcomes the opportunity to provide comments on the ICER *2020 Value Assessment Framework*. Alnylam is a biopharmaceutical company that develops and commercializes ribonucleic acid interference (RNAi) therapeutics. We believe in delivering transformative medicines for life-threatening diseases and good value to patients, providers, payers and society.

We actively engage in conversations about value by working alongside payers and through commitments in our [Patient Access Philosophy](#). We also participated in ICER's review of therapies to treat hereditary transthyretin (hATTR) amyloidosis in 2018. However, Alnylam is concerned that ICER's current value framework may have the unintended consequence of restricting access to life-changing treatments for patients.

In response to ICER's recent call for feedback, we have carefully reviewed ICER methods based on value framework documents. In the communication that follows, we have focused on five key areas for improvement. In particular, we recommend that ICER:

- 1. Better capture the patient perspective by reporting direct patient commentary on disease burden, unmet need, and treatment benefits, harms, and uncertainties, and prioritize formal adoption of a patient-focused value framework.**
- 2. Realign its topic selection process to take a broader and better targeted view of the best available opportunities to improve health system efficiency and fairness.**
- 3. Use budget impact as the primary method to assess rare disease treatments, to limit the potentially harmful consequences of inappropriately using cost-effectiveness analysis (CEA) as a price-setting tool in rare and ultra-rare diseases.**

4. **For all interventions under review, offer a concise, narrative summary of key evidence – rather than a single summary evidence matrix rating – to inform stakeholder decision-making.**
5. **For all interventions requiring CEA, more accurately account for pharmaceutical pricing dynamics (including generic entry) and valuation of future QALYs, to avoid undervaluing innovation and thus inappropriately limiting access to new therapies.**

Recommendation 1: Better capture the patient perspective by reporting direct patient commentary on disease burden, unmet need, and treatment benefits, harms, and uncertainties, and prioritize formal adoption of a patient-focused value framework

Patients are the single most important stakeholder in our healthcare system. They directly face the risk of death, loss of physical and / or emotional well-being, and impaired quality of life due to disease. Moreover, they are the end-users of healthcare products and services and the ultimate source of funding for these products and services (e.g., through insurance premiums and taxes).¹ It is clear that the patient viewpoint should have a central role in healthcare decision-making.

The current ICER value framework aims to incorporate the patient voice by soliciting patient input on topic selection, scoping, and evidence reports. Despite these efforts, ICER evidence reports remain more oriented toward a purely clinical and economic – rather than patient-focused – view on product value. A recent analysis found that 16% of patient comments on ICER draft evidence reports are incorporated into final evidence reports, compared with 33% of comments from other stakeholders.² Similarly, final evidence reports (typically over 100 pages in length) often feature a relatively limited overview of patient insights (most notably, approximately 1 page in the executive summary and 1 page in the report body, summarized through the lens of ICER reviewers).

ICER evidence reports should more clearly and directly reflect the importance of the patient perspective. We recommend that ICER solicit in-depth, patient-authored commentary on 1) disease burden and unmet need, 2) the meaning of demonstrated and potential treatment-related benefits and harms, and 3) how the benefits of treatment weigh against the harms, in view of unmet need and uncertainty. Such commentary should be given similar prominence and space relative to ICER reviewers' commentary on disease background and comparative clinical effectiveness. Over the longer term, we recommend that ICER prioritize evaluation and adoption of a patient-focused value framework, such as the Patient Perspective Value Framework,³ to ensure that value is formally and robustly assessed from the patient perspective.

Recommendation 2: Realign ICER topic selection to take a broader and better targeted view of the best available opportunities to improve health system efficiency and fairness

Since 2006, ICER has set out to inform policy decisions that “lead to a more effective, efficient, and just healthcare system.”⁴ We agree with this mission in principle but have concerns about how it is pursued in practice, with a disproportionate focus on orphan drugs and pharmaceuticals more broadly. Opportunities to make the US healthcare system more effective, efficient, and fairer extend well beyond pharmaceuticals. In fact, total US healthcare spending encompasses^{5,6,7}

- **hospital care:** ~30% of total US healthcare spending
- **physician / clinical services:** ~15% of total US healthcare spending
- **prescription drugs:** ~15% of total US healthcare spending (orphan drugs, 1% – 2%)
- **other care (e.g., dental care, medical equipment, etc.):** ~40%

These figures, together with the reality that non-pharmaceutical interventions are often not supported by the level of evidence routinely required from prescription drugs,^{8,9} indicate a tremendous opportunity: Critical evaluation of high-budget interventions beyond prescription drugs could have a transformative impact, making healthcare more effective, sustainable, and just. Despite this, among completed ICER reviews documented on www.icer-review.org¹⁰:

- Approximately 67% have involved pharmaceutical products (orphan therapies, ~23%)
- Approximately 44% have involved non-pharmaceutical interventions

These statistics highlight the need to realign the ICER topic selection process to more closely parallel the breakdown of US healthcare spending, to better target the largest opportunities to drive positive change. Accordingly, we propose that the process be revised so that the products and interventions reviewed by ICER better reflect the distribution of US healthcare spending across categories. Specifically, out of the total budget impact of products and interventions reviewed by ICER in a given year, we recommend that pharmaceuticals and non-pharmaceutical products / interventions account for 15% – 25% and 75% – 85%, respectively. Under this realignment, non-pharmaceutical interventions would be selected more often as a topic for evaluation. Pharmaceuticals would continue to be a potential area of assessment, but in a manner proportional to their impact on the US healthcare system.

Alnylam is committed to doing its part toward responsible stewardship of the US healthcare system. It is essential, however, that this responsibility be appropriately distributed across stakeholders in the healthcare system. Similarly, it is essential that ICER’s efforts to drive accountability focus on areas where the greatest positive impact can be made.

Recommendation 3: Use budget impact as the primary method to assess rare disease treatments, to limit the potentially harmful consequences of inappropriately using CEA as a price-setting tool in rare and ultra-rare diseases.

CEA is not an appropriate price-setting tool for rare disease treatments, for four key reasons: (i) high uncertainty over willingness-to-pay thresholds, (ii) failure to incorporate sources of value uniquely relevant to rare diseases, (iii) failure to quantify high-value aspects of rare disease treatments, such as unmet need, and (iv) the danger of eliminating motivation to develop rare disease treatments.

Society’s value of a QALY gained for rare diseases is highly uncertain

Society uniquely values treatments for serious rare diseases, due to considerations such as equity (i.e., ensuring all patients have the same access to treatment, no matter how rare or common their condition), “fair innings” (the principle that every human is equally entitled to a reasonable lifespan), the value of hope, and the rule of rescue (i.e., duty to rescue individuals at risk of avoidable death).¹¹ This is borne out by ample real-world evidence that decision-makers value QALY gains more for rare, severe diseases than for common, less severe ones.^{12,13} Along similar lines, public payers routinely make exceptions to cost-effectiveness determinations in reimbursing orphan drugs.^{14,15}

What is unclear is precisely how much more valuable QALY gains are in rare diseases, and how this varies with disease prevalence, severity, and unmet need. As a result, there is no basis to use an incremental cost per QALY threshold to inform price guidance in rare diseases. It simply cannot be assumed that any such threshold accurately reflects societal willingness to pay for health gains.

Novel sources of value are not included in the current ICER framework and CEA

Economic research has explored approaches to quantify components of value not typically captured by standard QALY-based CEA. These novel sources of value from medical innovation include:

- (a) *Insurance value*: Individuals tend to value QALY gains more highly in more severe and/or less prevalent diseases.¹³
- (b) *Equity*: Individuals tend to more highly value treatments that provide large health gains to fewer individuals with higher disease burden (vs. small health gains to more individuals with lower burden).^{16,17}
- (c) *Alleviation of caregiver burden*: Caring for individuals with rare diseases poses significant financial, social, and emotional challenges to family members; treatments for rare diseases may alleviate these challenges (in addition to improving the health of the affected patient).^{16,18,19}

These components of value are difficult to appraise and quantify accurately, so it is understandable that they are not always quantitatively included in ICER's standard value framework. However, failing to account for such important considerations inevitably leads to an inflated incremental cost-effectiveness ratio, further limiting the usefulness of CEA to set prices for rare disease therapies.

In diseases with high unmet need, comparator treatment costs unfairly influence CEA

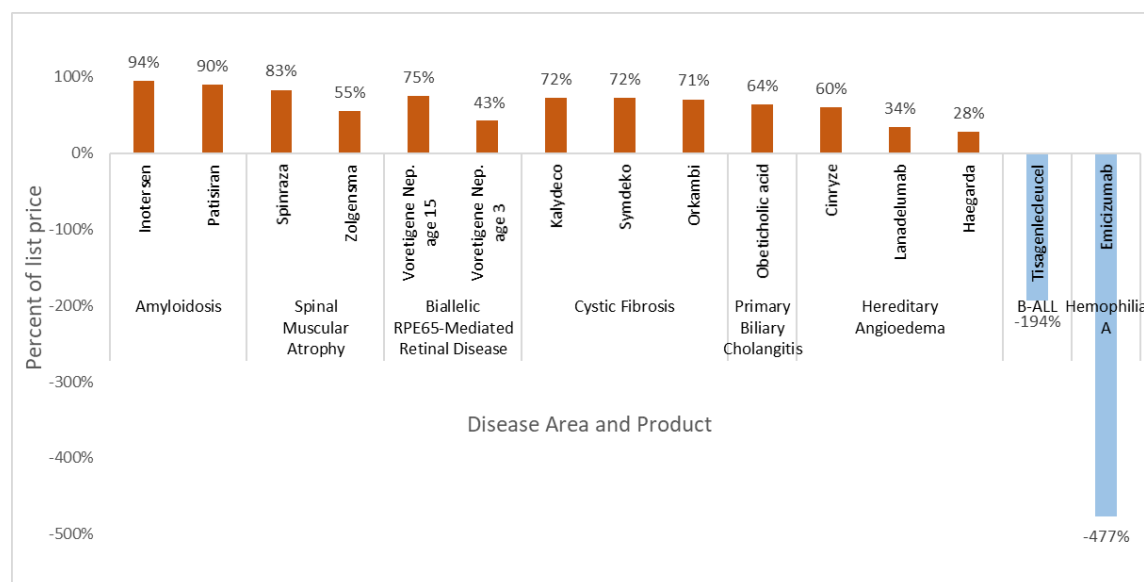
Because ICER's value framework measures a treatment's incremental costs and benefits relative to existing comparators, new therapies for rare diseases with few or no available treatments face an "unmet need trap."¹⁶ This trap occurs when a lack of past research and investment leaves patients with an inexpensive, ineffective standard of care as a comparator. The result is a large relative penalty on ICER's value-based price on any new therapy for diseases with few available treatments. On the other hand, treatments for diseases with a high-cost "legacy" standard of care comparator are rewarded – in a way that may be disconnected from their true value – under ICER's standard framework.

The impact is evident in previous ICER analyses in rare diseases (Fig. 1). Only two rare disease therapies were not recommended for price reduction: tisagenlecleucel (B-cell acute lymphoblastic leukemia), whose comparator had discounted lifetime costs of over \$300,000,²⁰ and emicizumab (hemophilia A), whose comparator had lifetime costs of over \$90 million.²¹ In contrast, CEA of nusinersen (spinal muscular atrophy) used a supportive care comparator with \$0 in drug costs. It is clear from these examples that CEA inadvertently places high value on the whims of medical history.

Price discount recommendations could adversely influence drug development (while failing to yield system-wide efficiency gains)

ICER's CEA-based price recommendations have an unintended negative consequence of disincentivizing development of new rare disease therapies. Price-setting according to ICER's value-based thresholds would potentially make drug development non-viable for most orphan drugs. ICER has recommended discounts for 12 of the 14 rare disease treatments it has reviewed, with a median discount of 64%. Dubois et al. found that a 10% increase in market size increases innovation by 2.3%.²² This implies that \$2.5 billion of additional lifetime revenue is needed to bring one new drug to market. Such a threshold for drug viability suggests that application of the ICER CEA framework to set drug prices could dramatically reduce the availability of breakthrough treatments for rare disease. This is a severe negative outcome without any clear accompanying gain in health system efficiency, given the limitations of CEA for setting prices of rare disease therapies.

Figure 1: ICER-calculated discount to reach \$150,000 per QALY threshold



Our recommendation is that ICER treat any CEA in a rare disease area as a supplemental analysis that does not inform pricing, due to the weaknesses (and potential harms) outlined above. Instead, ICER should evaluate rare disease therapy prices using ICER’s affordability criteria and specific country budgets, as affordability is what truly affects health system sustainability for rare diseases. ICER should also conduct additional research on society’s willingness-to-pay, in the context of rare diseases, as well as frameworks that appropriately capture the true value of rare disease treatments.

Recommendation 4: For all interventions under review, offer a concise, narrative summary of key evidence – rather than a single summary evidence matrix rating – to inform stakeholder decision-making.

While a comparative review of clinical effectiveness of healthcare interventions is valuable, using the ICER Evidence Rating Matrix to reduce the full body of evidence to a single summary rating raises significant concerns. Subjectivity is the key concern. The voting process recorded in ICER reports often reveals disagreement and idiosyncrasy in how evidence is assessed, while the ICER Evidence Rating Matrix users’ guide refers to imprecise constructs such as “conceptual confidence intervals.” Likewise, the users’ guide notes that “a small difference in a quantitative score may be considered clinically significant in multiple directions, or not significant at all,” and that “[d]isagreements about the assessment of each domain and of the overall level of certainty are certainly likely, even among reviewers in the same group.”²³

A further concern is that the ICER evidence rating matrix does not consider the cost of increasing evidence quality. While increasing evidence quality is clearly beneficial, taking time to gather more evidence from larger and longer trials jeopardizes patients’ health and access to possible life-saving treatments.^{24,25} Acknowledging this, the FDA recently approved Project Facilitate, an access program for unapproved cancer medications.²⁶ The project explicitly recognizes that the benefits of increasing evidence quality should be balanced with the cost to patients of delays in access due to scientific and bureaucratic protocols. This issue is of particular relevance in rare diseases, where (by definition) evidence is more difficult to acquire. Policy makers, HTA bodies, and other experts have repeatedly expressed concern with the evidence evaluation process for rare disease therapies.^{27,28,29}

Finally, ICER’s summary evidence rating does not have a practical application in the ICER framework. The current framework yields price targets based solely on CEA results. The presumed rationale is that CEA already implicitly, quantitatively accounts for the concepts captured by the evidence rating matrix: comparative efficacy and safety and the uncertainty in these two parameters. However, this reinforces that a

composite summary rating of comparative clinical effectiveness and data uncertainty is redundant, with minimal practical value to inform decision-making.

Despite these concerns, we recognize the central role of clinical data in healthcare decision-making, and the way in which it complements economic data in payer decision-making. (For example, NICE appraisals may allow for standard ICER thresholds to be relaxed for highly innovative interventions that offer a “step-change” over standard of care.³⁰) We therefore recommend that ICER continue to systematically evaluate relevant evidence for interventions under review and use this to generate a high-level narrative summary of unmet needs, strength of evidence, and degree of certainty around benefits and risks. However, we recommend that ICER no longer assign a single summary rating, as this headline result creates a false sense of precision and discourages more nuanced assessment of evidence and unmet need by healthcare decision-makers.

Recommendation 5: For all interventions requiring CEA, more accurately account for pharmaceutical pricing dynamics (including generic entry) and valuation of future QALYs, to avoid undervaluing innovation and thus inappropriately limiting access to new therapies.

Research has shown that when generic or biosimilar competition enters the market, drug prices will decrease, often substantially. A review of top-selling small molecule generics found price declines of 83% to 95%,³¹ while branded biologics declined by 20% to 30%.³² ICER’s model explicitly disregards these decreases, which significantly increases the lifetime costs of treatments and inflates incremental cost-effectiveness ratio estimates. Studies have verified the importance of considering the dynamic nature of drug prices when evaluating cost effectiveness.^{33,34,35}

The current ICER framework also ignores the dynamic nature of QALYs, whose value grows as expected real incomes rise. The economic literature has demonstrated that fair valuation of future QALYs requires treating them differently from measures of financial cost – for example, by discounting them at a lower rate. Belgium, the Netherlands, and Poland currently recommend differential discounting,³⁶ as does recent guidance from the Treasury of the United Kingdom.³⁷

The ICER framework should begin to reflect the reality of pricing dynamics over extended time frames. Therefore, it is recommended that the ICER model base case include decreases in therapy price due to competition and generic entry. ICER should also determine an appropriate method to account for changes in the value of future QALYs – for instance, by incorporating projected growth rates in gross domestic product and modeling changing QALY valuations over time.

Conclusion

We would like to thank ICER for the opportunity to contribute to the development of the *2020 Value Assessment Framework*. We believe our suggestions will help improve the evaluation of healthcare products and interventions and, in turn, allow our society to address unmet needs through increased innovation and access to effective and appropriate care.

References

- ¹Seidman J, et al. Measuring value based on what matters to patients: a new value assessment framework. Available from: <https://www.healthaffairs.org/doi/10.1377/hblog20170523.060220/full/>. Accessed June 6, 2019.
- ²Partnership to Improve Patient Care, XCenda. Responding to Stakeholder Input: Finding the Patient Voice in ICER's Value Assessments. Available from: <https://www.xcenda.com/-/media/assets/xcenda/english/content-assets/white-papers-issue-briefs-studies-pdf/pipc-xcenda-icer-stakeholder-mapping-final-report-2018.pdf?la=en&hash=FCA2BC11D566FE0A69E8C2DCC6423DFCDA4A622B>
- ³Avalere / FasterCures. Patient-Perspective Value Framework (PPVF): Version 1.0. Available from: <https://www.fastercures.org/assets/Uploads/PPVF-Version-1.0-Methodology-Report-Final.pdf>
- ⁴Institute for Clinical and Economic Review. About ICER. Available from: <https://icer-review.org/about/>. Accessed May 20, 2019.
- ⁵Center for Medicare & Medicaid Services. National Health Expenditure Accounts: National Health Expenditures 2017 Highlights. Available from: <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/highlights.pdf>. Accessed May 20, 2019.
- ⁶IQVIA Institute for Human Data Science. Medicine Use and Spending in the US. 2018. IQVIA: Parsippany, NJ.
- ⁷QuintilesIMS Institute. Orphan Drugs in the United States. 2017. QuintilesIMS Institute: Parsippany, NJ.
- ⁸Vliet Vlieland TPM. Non-drug care for RA—is the era of evidence-based practice approaching? *Rheumatology*. 2007;46:1397–1404.
- ⁹Al-Lamee R, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391:31-40.
- ¹⁰Institute for Clinical and Economic Review. ICER: Completed Assessments. Available from: <https://icer-review.org/topics/#past-topics>. Accessed May 20, 2019.
- ¹¹Doctor J, MacEwan JP. Limitations of traditional health technology assessment methods and implications for the evaluation of novel therapies. *Curr Med Res Opin*. 2017;33:1-8.
- ¹²Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. *BMJ: British Medical Journal*. 2004;329:224
- ¹³Shah KK. Severity of illness and priority setting in healthcare: a review of the literature. *Health Policy*. 2009;93:77-84.
- ¹⁴Wang A, et al. US payer perspectives on evidence for formulary decision making. *J Oncol Pract*. 2012;8(3S):22s-27s.
- ¹⁵Pant S, Visintini S. Drugs for rare diseases: a review of national and international health technology assessment agencies and public payers' decision-making processes. *CADTH Environmental Scan*. 2018(77).

-
- ¹⁶Jena A, Lakdawalla D. Value frameworks for rare diseases: Should they be different? *Health Affairs Blog*. 2017;12.
- ¹⁷Lakdawalla DN, et al. Defining elements of value in health care—a health economics approach: an ISPOR Special Task Force report. *Value Health*. 2018;21:131-139.
- ¹⁸Schlander, M., et al., *Incremental cost per quality-adjusted life year gained? The need for alternative methods to evaluate medical interventions for ultra-rare disorders*. Journal of comparative effectiveness research, 2014. 3(4): p. 399-422.
- ¹⁹Paulden M, et al. Value-based reimbursement decisions for orphan drugs: a scoping review and decision framework. *Pharmacoeconomics*. 2015;33:255-269.
- ²⁰*Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value: Final Evidence Report*. Institute for Clinical and Economic Review.
- ²¹*Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value*. Institute for Clinical and Economic Review.
- ²²Dubois P, et al. Market size and pharmaceutical innovation. *RAND J Econ*. 2015;46:844-871.
- ²³Institute for Clinical and Economic Review. ICER Evidence Rating Matrix: A User's Guide. Available from: <http://icer-review.org/wp-content/uploads/2016/02/Rating-Matrix-User-Guide-UPDATED-06.30.17.pdf>. Accessed May 29, 2019.
- ²⁴Lakdawalla DN, et al. Evaluating expected costs and benefits of granting access to new treatments on the basis of progression-free survival in non–small-cell lung cancer. *JAMA Oncol*. 2015;1:196-202.
- ²⁵Bognar K, et al. The role of imperfect surrogate endpoint information in drug approval and reimbursement decisions. *J Health Econ*. 2017;51:1-12.
- ²⁶US Food and Drug Administration. FDA announces Project Facilitate to assist physicians seeking access to unapproved therapies for patients with cancer. Available from: <https://www.fda.gov/news-events/press-announcements/fda-announces-project-facilitate-assist-physicians-seeking-access-unapproved-therapies-patients>. Accessed June 7, 2019.
- ²⁷Gutierrez L, et al. Principles for consistent value assessment and sustainable funding of orphan drugs in Europe. *Orphanet J Rare Dis*. 2015;10:53.
- ²⁸Rosenberg-Yunger ZR, et al. Priority setting for orphan drugs: an international comparison. *Health Policy*. 2011;100:25-34.
- ²⁹Hughes-Wilson W, et al. Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? *Orphanet J Rare Dis*. 2012;7:74.
- ³⁰National Institute for Health and Care Excellence (UK). Single technology appraisal: User guide for company evidence submission template. Available from: <https://www.nice.org.uk/process/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-72286715419333>. Accessed June 6, 2006.
- ³¹Association for Accessible Medicines. *Generic Drug Access & Savings in the US*. Washington, DC: AAM, 2017.
- ³²Mulcahy AW, et al. Biosimilar cost savings in the United States: initial experience and future potential. *Rand Health Q*. 2018;7.
- ³³Lu Y, et al. Dynamic cost-effectiveness of oncology drugs. *Am J Manag Care*. 2012;18(11 Suppl):S249-256.

³⁴Garrison LP. Rewarding value creation to promote innovation in oncology: The importance of considering the global product life cycle. *Oncologist*. 2010;15(Supplement 1):49-57.

³⁵Lakdawalla D, et al. What do pharmaceuticals really cost in the long run? *Am J Manag Care*. 2017;23:488-493.

³⁶Attema AE, et al. Discounting in economic evaluations. *Pharmacoeconomics*. 2018;36(7):745-758.

³⁷HM Treasury. *The green book: Central government guidance on appraisal and evaluation*. Available from:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/685903/The_Green_Book.pdf. Accessed May 29, 2019.



**The American Legion
Department of California**

1601 7th Street

Sanger, CA 93657

Phone (559) 875-8387 Fax (559) 272-5157

www.calegion.org

Larry Leonardo, Commander

Paul Brown, Adjutant

June 7, 2019

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

Dear Dr. Pearson,

As organizations representing veterans and individuals in the military living with diverse conditions and diseases, as well as their families, caregivers and providers, we are pleased to provide feedback on the Institute for Clinical Economic Review (ICER) 2020 Value Assessment Framework.

On June 27, 2017, ICER announced an agreement to work with the Department of Veterans Affairs (VA) Pharmacy Benefits Management Services office (PBM) to support its use of ICER drug assessment reports.¹ As we understand, under this agreement, ICER is working with VA staff to integrate ICER's academic reports into the VA formulary management process of evaluating the comparative effectiveness and value of drugs. Therefore, for us, updating ICER's value framework holds particular significance due to its influence over the care that veterans and members of the military are able to access.

ICER Should Abandon the Discriminatory Quality-Adjusted Life Year and Similar Metrics

ICER utilizes a quality-adjusted life year (QALY) metric as the basis for its value assessments that is very controversial for its discriminatory impact on people with disabilities and serious chronic conditions. The QALY inherently discriminates against patients and people with disabilities by placing a lower value on their lives. In fact, in 1992, the U.S. Department of Health and Human Services denied a state waiver application after determining the use of QALYs in Medicaid would be discriminatory and potentially violate the Americans with Disabilities Act (ADA).² Also, Medicare has a statutory ban against use of QALYs and similar metrics for coverage decisions.³ We have significant concerns that similar protections against the use of a cost-per-QALY value assessment do not exist for our members. It is profoundly unfair and offensive to those who have served this country to allow for this kind of discrimination in the veterans health system. Therefore, we urge ICER to abandon the use of the QALY in its value assessments and instead work toward more patient-centered strategies for assessing value that are not based on averages so that our Veterans' health system is not susceptible to this kind of discrimination.

¹ See <https://icer-review.org/announcements/va-release/>

² See <https://www.nytimes.com/1992/09/01/opinion/l-oregon-health-plan-is-unfair-to-the-disabled-659492.htm>

³ 42 USC Sec 1320e, 2017. Accessed December 4, 2018.

ICER's Value Framework Should Better Reflect the Value of Treatments for Individuals

Under the existing methodology, ICER's value determinations are based on population-level averages that do not reflect individual differences among veterans. Additionally, ICER tends to conduct their value assessments at a stage when inadequate data is available to reflect subpopulations, specially veterans in particular. No veteran is average and treating them as such only undermines the clinical knowledge of providers in the veterans' health system that may not yet be reflected in the research. We are concerned that the use of ICER's assessments will further limit access to care tailored to individual veterans, thereby exacerbating the existing access challenges that they and their caregivers often face. In an era when policy-makers and stakeholders want to improve care to veterans, the VA's health system should embrace patient-centeredness, as opposed to becoming entrenched in a one-size-fits-all perspective of health care value. Different people respond differently to the same drugs and no two veterans are the same or have the same health care needs. Each veteran deserves care from a health system that recognizes his or her unique needs and characteristics.

Any ICER Value Assessment Used by the VA Must Incorporate Feedback from Veterans

ICER's research is often criticized by patients for failing to incorporate their input or focus on the outcomes that matter to them. We are unaware of ICER surveying veterans for information about the outcomes that matter most to them or the goals for their treatment. Certainly, we have not been directly engaged in the development of any value assessments conducted by ICER for the VA's use in developing their formularies. Veterans have unique health challenges that cannot be averaged out alongside civilian populations. The point of a health system managed by and for veterans is to ensure that there exists an infrastructure for treating veterans with disabilities and serious chronic conditions that is responsive to their unique needs and characteristics. Without specific engagement of veterans, ICER cannot develop a value assessment that would be constructive for use by the VA to achieve outcomes that matter to veterans in the real world.

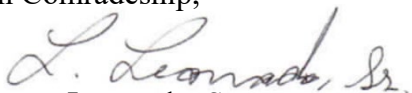
Care that Fails Veterans Leads to Higher Costs

Standardized care decisions create barriers to certain treatments for veterans that don't meet "average" thresholds, leading to increased costs when treatments fail the patient. When patients cannot access treatments that work for them, the VA system bears the cost of reduced treatment adherence, increased hospitalization and other acute care episodes, as well as the societal costs of increased disability over time. In this age of personalized medicine, we want the VA to rely on expertise that will drive the agency to reduce costs and improve care quality by better targeting treatments shown to work on patients with similar characteristics, needs and preferences, thereby avoiding the waste of valuable resources on care that veterans do not value.

In conclusion, prescription drug coverage determinations based on ICER's currently flawed analyses are not the answer and can only serve to further limit access to care for veterans with disabilities and serious chronic conditions, thereby exacerbating the challenges that they and their caregivers often face. We want ICER's value framework to be updated in a manner that would constructively assist VA to be a model for putting patients first by engaging patients. Otherwise, it is not appropriate for the VA to be referencing ICER's studies at all.

Thank you for this opportunity to comment. In light of your direct relationship with the VA, we hope that you will act on our recommendations.

In Comradeship,



Larry Leonardo, Sr.

State Commander, Dept of California
The American Legion

**America's Health
Insurance Plans**

601 Pennsylvania Avenue, NW
South Building
Suite Five Hundred
Washington, DC 20004

202.778.3200
www.ahip.org



June 21, 2019

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

Submitted electronically via publiccomments@icer-review.org.

RE: *Public Input for 2020 Value Assessment Framework Update*

Dear Dr. Pearson:

Thank you for soliciting public input on how to improve the Institute for Clinical and Economic Review's (ICER) value assessment framework. America's Health Insurance Plans (AHIP) and its members are committed to ensuring that everyone has affordable coverage that provides them with access to high-quality care. With this commitment in mind, we appreciate the opportunity to provide feedback, and we commend your efforts to regularly update the approach.

ICER's value assessment framework is the backbone of ICER's analyses. It ensures that ICER's conclusions are supported by a rigorous, transparent process, a robust evidence base, and input from a broad array of stakeholders. With this value assessment framework, we are all positioned to work together more effectively for sustainable high-value care for all patients.

This is particularly important for prescription drugs, where manufacturers frequently set extremely high and unsubstantiated launch prices for new drugs and that result in higher costs of health care for everyone. ICER's framework is essential as we continue to see increasingly expensive treatments and therapies enter the market, some lacking a strong evidence base that helps us understand their value and how to make them more affordable to patients and consumers.

Cost-Effectiveness Thresholds ICER Uses

We agree that patients with ultra-rare diseases deserve treatments that will work for them. But the most groundbreaking treatments do no good for anyone if no one can afford them. That's why we support the use of cost-effectiveness thresholds to establish value-based price benchmarks for treatments of both common and ultra-rare diseases. Quantitative outcomes must be at the core of ICER's assessments.

Moving away from clinical outcomes and towards surrogate endpoints - or even simply mechanisms of action - would set a dangerous precedent for patients. For example, a recent article in *JAMA* found that many

breakthrough cancer drugs actually did not meaningfully extend life for patients.¹ Patients deserve better. They deserve the confidence of knowing that the medications they pay for are likely to work.

Evaluating Net Health Benefits, and How to Incorporate Real-World Evidence

We generally support the approach ICER takes to use clinical evidence to evaluate the magnitude and certainty of net health benefits. However, real-world evidence should not be considered with the same weight as quantitative data. We need improvements in data collection and quality for real-world data before it can be significantly relied on for evaluating net health benefits. The patient perspective and qualitative elements should both be highlighted in evaluations. But it is too soon to put forth a robust plan to incorporate real-world evidence into the assessment framework.

Use of Both QALY and evLYG to Evaluate Degree of Improvement in Health Outcomes

We support the use of Quality-Adjusted Life Years (QALY), and Equal Value of Life Years Gained (evLYG) for rare diseases in particular, as the use of evLYG complements the use of QALY. This multifaceted analytic approach can provide policymakers with helpful and practical information to support the development of evidence-based policies.

Methods to Integrate Potential Benefits, Context, and Other Factors Relevant to Value

It's worth considering potential benefits, contextual considerations, and other factors to assess an intervention's value. We support the consideration of a list of qualitative improvements when assessing value. However, these are not vetted relative to clinical function or improvement – therefore they should be divorced from the actual thresholds used during value assessments.

Conclusion

We appreciate the opportunity to provide feedback and look forward to continued discussions with you on how we can help drive better affordability and access to prescription drugs for every American.

Sincerely,



Kate Berry
Senior Vice President

¹ Gyawali, B., Phillips Hey, S., Kesselheim, A. "Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval." *JAMA Intern Med.* May 28, 2019. doi:10.1001/jamainternmed.2019.0462.

AHIP is the national association whose members provide coverage for health care and related services to millions of Americans every day. Through these offerings, we improve and protect the health and financial security of consumers, families, businesses, communities, and the nation. We are committed to market-based solutions and public-private partnerships that improve affordability, value, access, and well-being for consumers.

Overview

Amgen appreciates the opportunity to provide input for ICER's *2020 Value Assessment Framework*. Our comments are informed by our experience engaging in ICER assessments since late 2015 and are intended to support the evolution of ICER's framework to better align with scientific best practices.

We acknowledge ICER's mission is *"to help provide an independent source of analysis of evidence on effectiveness and value to improve the quality of care that patients receive while supporting a broader dialogue on value in which all stakeholders can participate fully."*¹

The credibility and impact of ICER as an independent value assessment body seeking to provide evidence aimed at improving patient quality of care and dialogues on value, hinges on a firm grounding in robust and transparent science, methods, and processes. The US can benefit from rigorous systematic assessments of new technologies to help stakeholders better understand the value of new interventions. We appreciate the steps ICER has taken to refine its value assessment framework over time, and ICER's openness to further changes. Our comments are focused on changes that we believe are necessary to move ICER's current framework towards a more reliable and valid approach that better aligns with its stated mission to enable more objective and robust dialogues on value. Our comments cover three areas:

1. Process
2. Methods
3. Special considerations.

The Amgen team is available to further share detailed observations and insights in support of the below recommendations as needed. ICER's 2020 Value Assessment Framework has the opportunity to become an evaluation process that is more systematic, transparent, objective, and scientifically robust with continued changes to the existing framework, and we are hopeful that ICER will make the necessary changes to move towards this standard.

1. PROCESS

(i) Objectivity, Reliability, and Transparency

As an advisor to US healthcare stakeholders, the value of ICER's contributions relies on its objectivity, reliability, and transparency. This is especially true in a fragmented payer system where it is impossible for value assessment bodies such as ICER to have accountability to multiple budget holders, or liability for the patients potentially impacted by its recommendations. The complexity of the US healthcare system is reflected by the diversity in payers with differing appraisal processes, as evidenced in an observed variation in formularies.² Results of independent value assessments will be more credible if the approach used is objective and consistent, and the findings are broad such that they may be adapted based on the needs of individual payers. Whether it is an assessment group for a single payer, the FDA or an individual US insurer's assessment group, these bodies universally recognize that organizations making decisions that affect the quality of health or survival of a given group of patients are also subject to legitimacy, regulation, and accountability. It is not without reason that governments set this accountability, as it is necessary and frequently exercised in practice.^{3,4,5,6,7} For example, when the FDA makes a decision to approve a new drug, it is directly accountable to the

US government with extensive regulations, audits, and procedures that help to ensure its evaluations are credible, consistent, and as robust as the available evidence base allows. Value is a highly subjective concept, and independent organizations conducting value assessments in the US, such as ICER, should demonstrate an approach that is objective, reliable, and reproducible (*i.e.*, fully transparent), with measures to ensure these qualities are reflected in practice, such as external audits and internal reviews.

Recommendation: As an independent organization that makes its reports public to inform discussions on value, ICER's approach needs to be objective, reliable, and transparent, with measures in place to monitor this and take corrective action when appropriate.

- Taking an objective, unbiased stance enhances credibility. This means equally considering different stakeholder input, providing full transparency and rationale behind decisions and methods deviations, reporting results in a fair and balanced manner based on the available evidence, and avoiding citing personal views or opinions as facts. Objectivity is also demonstrated by presenting multiple perspectives (health system and patient) and a range of analyses based on different assumptions, rather than anchoring the evaluations to a base case from the perspective of a single type of payer. Another key area where ICER can be more objective is when moderating appraisal committee meetings, as subjective statements or opinions (as innocuous as they may seem) have had and will continue to have a strong impact on influencing panel outcomes.
- Adhering to a consistent, reliable approach will further lend itself to being trusted. ICER has several good mechanisms in place that follow a sound approach, such as posting a topic, followed by scope, and then the report. A key area of focus is providing consistency in approach with ICER published methods and protocol, and when deviations are needed, publicly disclosing amendments in a timely manner with a clear rationale. Health technology assessment (HTA) is a dynamic process and changes are inevitable; however, these changes need to be managed systematically and transparently to yield a reliable process that may be replicated.
- Offering full transparency fosters greater trust and credibility. Across all initiatives, ICER should make its process, research methods, assumptions, data inputs, and equations available in a completely transparent manner, such that results are fully reproducible by third parties and reviewed by known experts as part of the assessment. We also suggest that ICER implement a process allowing for external, independent validation of economic model structure, inputs/assumptions, and results. ICER has made some advances towards transparency and fostered candid discussions with stakeholder parties on this topic. We encourage ICER to seek out collaborative model agreements that are free from privacy/intellectual property constraints to enable third parties to validate key aspects of its economic analyses, especially given that the outcome is intended as a public good.

(ii) Appraisal Committee Composition

As the key body of stakeholders deliberating at ICER's Public Meetings, the voting panel should include those with relevant expertise and represent those directly impacted by its recommendations for a given disease area. Patients are the end consumer and arguably the most important stakeholder for any assessment of health and treatment value. Payers, physicians, and manufacturers are other stakeholders that may be directly impacted by the panel results. A May 2019 analysis of ICER's 3 voting panels (CTAF, New England CEPAC, and Midwest CEPAC) found that most members are in the academic field, while there are very few patient advocates. Of the 59 voting members across the 3 panels, 70% were academics, 9% were payers, and only 7% were patient advocates.⁸ It is a concern that patients in this process are often passengers with highly limited involvement in decisions that most personally impact them. In addition, the patient advocates currently included on ICER's panels do not represent the views and perspectives of a typical patient that would be impacted by that assessment (for example a male oncology patient representative on a migraine panel is unlikely to be able to empathize with the burden of a female migraine patient). It is very hard for those who have not directly experienced the condition as a patient or treated it as a physician to provide an informed judgement on treatment value. Furthermore, there are no manufacturers or disease experts on the voting panel. More relevant discussions and appropriate decisions could be made by the panel by adding voices of informed individuals and groups. In addition, it is important that panelists are held to ethical standards with clear expectations and a code of conduct for preparations, involvement, and interactions leading up to and throughout the appraisal meeting. The panel moderator should assume an impartial and objective stance and hold the panelists accountable to the appropriate code of conduct.

Recommendation: ICER's voting panels should include relevant patient advocates, disease experts, physicians, and manufacturers. A code of conduct regarding panelist expectations and panel moderation should be publicly available. ICER has made progress on its overall stakeholder engagement approach and should continue to engage all relevant stakeholders early on and throughout its process, including panel voting.

(iii) Impact Monitoring

Based on ICER's mission, the corresponding value assessments aim to improve overall patient quality of care, which suggests they should have a positive impact on improving patient access when treatments are "good value". To remain true to this mission, it is important that ICER's impact be equally favorable to reducing access hurdles for patients as they may serve as negotiation tools for payers. ICER's press releases communicate that products are "low value" without tethering the 'who' they are low value to – the insurer. In the present U.S. healthcare environment, this translates to cost-savings for the insurer, which the patients and the broader society does not benefit from. ICER assessments may be leveraged by payers in negotiations with manufacturers resulting in 1) greater use of prior authorization for patients and step-edits which can put significant delays in patients being able to access the treatments that their physicians believe are in their best interest and 2) placing drugs into higher tiers which could lead to greater cost falling to patients from co-payments and co-insurance rates.⁹ We appreciate instances where ICER has reported treatments to be "good value for money" and encouraged payers to provide access; although soft trends suggest there was no

improvement in access.¹⁰ We hope ICER will seize the opportunity to be an advocate for patient access through greater efforts working with payers to reduce access barriers when treatments are good value.

We encourage ICER to monitor the impact of its assessments on patients' ability to access treatment, and continue to refine its approach to better help patients achieve optimal quality of care. More research is needed to tie HTA presence and type of value framework or methodology to improvements in health delivery and overall healthcare outcomes.^{11,12} Without ongoing monitoring and refinements, value assessment outputs may have unintended consequences, causing harm to patients. There is a distinct lack of research on how HTA affects healthcare efficiency, budgets, and societal health outcomes.¹³ While other factors may be at work, much more research is needed on the impact of HTA and patient access.^{14,15} Furthermore, HTA in which cost-effectiveness is the key determinant of value has been observed to result in more restricted patient access compared to HTA where clinical evidence is the key determinant.¹⁶ Additionally, the impact of HTA is inconsistent across therapeutic areas.¹⁷ ICER and others looking to apply HTA in the US should first evaluate the impact of different types of HTA on patient outcomes, patient access, and affordability to avoid inadvertent effects on patient health status or financial burden on specific patient subgroups (e.g., subgroups that could take a greater role in ICER assessments, such as rare disease patients, pediatrics patients and caregivers).

Recommendation: We encourage ICER to become an advocate for patient access when treatments are good value, making greater efforts to work with payers to reduce barriers to access and monitor the impact of their findings to understand and learn from how their assessments are being used.

2. METHODS

i) QALY and evLYG

ICER should actively supplement the QALY as a starting point, with additional relevant data that is appropriately weighted, informed by patient and stakeholder inputs. Over-reliance on the Quality-Adjusted Life Year (QALY) as the sole outcome measure for assessing value will diminish the accuracy and applicability of the value assessments given the size and complexity of the US healthcare ecosystem. A dependence on cost-effectiveness introduces severe limitations in HTA decision making, omitting fundamental variables such as unmet need, patient vulnerability, and the potential of breakthrough treatment innovations. Health economic groups, including the ISPOR Special Task Force on US Value Assessment Frameworks, are attempting to identify alternative approaches to the QALY to better characterize value.¹⁸ The empirical application of the QALY is complicated by a multitude of challenges ranging from the inherent unreliability of these outcomes to discrimination in their application that could lead to decisions placing patients' health at risk. Key challenges are noted below:

- *QALYs have insufficient sensitivity to measure small but clinically meaningful changes in health status.* For example, QALYs disproportionately penalize patients with short life expectancies or reduced endurance limits and additionally, they do not accurately reflect patient preferences.¹⁹

- *QALYs cannot be derived for very young or very old populations.* An outcome should not be a function of the ability to elicit a utility (as in children and babies or use of caregiver proxies), and they should not be a function of lifespan.²⁰
- *QALYs are not consistent for all patients.* Patients with lower QALYs due to co-morbidities or with a chronic disease whose lives are extended will have overall higher/unfavorable incremental cost per QALYs than patients with mild disease. Additionally, QALY increments for patients at the lower end of QALYs will be more meaningful than those at the upper end.
- *QALYs are inappropriate for rare, life-threatening disease.* See the below section on rare disease.

ICER has introduced the equal value of Life Years Gained (evLYG) to help address a key issue flagged as a limitation of the QALY – undervaluing treatments that extend life but do not improve quality of life. Although the QALY is in much need of supplementation, and the evLYG ensures that years of life irrespective of health state are considered, it also introduces other limitations in that any changes in quality of life are ignored and it does not address many of the very significant methodological and practical inaccuracies of the QALY.

Recommendation: ICER should actively seek to supplement the QALY and evLYG with additional relevant data with appropriate weighting informed by patient and caregiver preferences, and expert input. Also, please refer to the contextual considerations section below.

(ii) Cost-Effectiveness (Incremental Cost-Per-QALY) Thresholds

Cost-effectiveness thresholds vary significantly based on context, and therefore must be flexible, updated periodically to reflect societal preference and the willingness to pay for care, and only established by budget holders to inform their decisions. We appreciate that ICER seems to accept that a single static threshold may not be the most appropriate approach, and hence, is seeking feedback on this topic. Given the complexities of the US healthcare system and extensive limitations of the QALY, ICER should abandon static cost-effectiveness (C/E) thresholds based on the incremental cost per QALY. Use of static C/E thresholds has consequences on patient outcomes and costs; while greater research is needed, there is evidence suggesting countries that apply static thresholds to decision making also have correlated poorer health outcomes. One study compared the impact of C/E thresholds in decision making for cancer drugs between five countries that use C/E thresholds and five countries that do not. The results showed that patients in countries that use C/E thresholds have both more restricted and delayed access to cancer drugs, with lower associated survival rates.²¹ ICER should carefully evaluate the possible impact of using static C/E thresholds in the US through the lens of how it could limit access to innovative, lifesaving treatments. ICER has a unique opportunity to deliver good service to decision makers in providing robust cost-per-QALY estimates, without framing these with highly subjective and static C/E thresholds.

Cost-effectiveness thresholds should represent broad ranges that are flexible enough to enable assessments to be appropriately tailored according to important contextual nuances. There is no scientific foundation to leverage a static \$50,000 to \$150,000 threshold to inform value-based prices, which is pulled from a contextually irrelevant and widely criticized WHO “benchmark” of one to three times per capita GDP, or to adapt thresholds from other countries given the fragmented US healthcare system where there are

no data to inform that the true opportunity cost of a new technology is at the margin of health spending.^{22,23,24,25,26,27,28} Appropriate C/E thresholds could range from as low as \$50,000 to greater than \$500,000 depending on a number of key contextual variables such as (a). *availability of treatments*, (b). *rule of rescue*, (c). *severity of condition*, (d). *prognosis*, (e). *societal fear*, (f). *impact to specific populations*, and (g). *information available to budget holder to optimize healthcare efficiency*. Examples of how C/E thresholds could vary from less than \$150,000 to greater than \$500,000 based on such variables include the following; however, one should keep in mind that C/E thresholds are inherently biased against the oldest and sickest patients, as well as those with rare diseases.

- *Less than \$150K/QALY*: This is less relevant for innovative treatments addressing areas of high unmet need. Generally lower thresholds are designed for less resourced countries or highly restrictive markets where tough trade-off decisions regarding resource allocation needs to be made. Lower thresholds may also be relevant to circumstances where the disease is common, prognosis is good, and patients are well-served through available treatment options, including generic standard of care. For example, screening and treatment for some types of clinical and subclinical disease as suggested by one researcher.²⁹
- *Greater than \$150K/QALY*: May be more relevant for innovative treatments where there is an unmet need. For example, this may be acceptable for some cardiovascular diseases depending on the incidence, patient disability, access issues and available alternatives.^{30,31}
- *Greater than \$250K/QALY*: May be more relevant for illnesses with high burden, poor prognosis or that are devastating in nature. For example, certain oncology treatments may have acceptable C/E threshold above \$250,000³².
- *Greater than \$500K/QALY*: Rare diseases likely command a C/E threshold of greater than \$500,000 based on a recent systematic review.³³ These diseases are characterized by extremely low incidence, few/no treatment options, poor prognosis without treatment, and high disease burden (e.g., paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, hemophilia, and Gaucher's disease).

We encourage ICER to empower the appraisal committee's contributions by enabling deliberation based on the available evidence, without the confines of a threshold that suggests what the voting results should be. The current assessment framework allows ICER's QALY threshold to overrule the panel's deliberation and disempowers the committee by automatically designating a 'low value' for treatments with an incremental cost per QALY above \$175K. This eliminates ICER's spirit and intent of a process initially designed to allow the committee to appropriately gauge the intangible costs of a disease and the nuanced benefits of each new treatment. It also removes the opportunity for the committee to rate promising new treatments any higher, limiting the committee's contribution. ICER has the opportunity to abandon this approach and recapture the full richness and patient relevance of contextual criteria reflected in its assessments, aided by a truly empowered independent public appraisal committee.

Recommendation: ICER should disaggregate estimates of cost effectiveness (incremental cost per QALY) from C/E thresholds and leave willingness to pay up to each respective decision maker instead of attempting to define it on behalf of the US public. We also encourage ICER to eliminate the C/E threshold constraints imposed upon the committee and directly include valuation methods in the framework and cost-effectiveness analysis that allow value and contextual considerations to have a greater impact.

(iii) Contextual Considerations

ICER's framework should be modified to place less weight on the QALY and enable more emphasis on capturing value based on important determinants from all stakeholder perspectives. It is well recognized by many experts that HTAs are limited by an overreliance on QALYs, which place too much emphasis on cost-effectiveness and willingness-to-pay thresholds to guide decision making, and alternative tools that provide a more holistic assessment of value are needed. ICER has a good starting point with its list of contextual considerations reviewed by the appraisal committee. However, based on the current approach, important determinants of value buried within contextual considerations largely sit 'outside' of the framework, where they have much less visibility and do not influence the quantitative analysis nor do these influence the panel vote. The treatment of these data obscure value determinants resulting in minimal or no impact on the ultimate assessment of value.

We encourage ICER to explore new methodologies with empirical application that is scientifically sound, robust, and validated. Several techniques are in development to more comprehensively capture aspects of value that include both health and non-health benefits such as wider public health effects, positive net tax flow, distribution of health, stimulation of medical innovation, peace of mind, and increased macroeconomic growth. Examples of methodologies in development and being tested are listed in the Appendix, and include multi-criteria decision-analysis (MCDA), augmented or extended cost-effectiveness analysis (ACEA/ECEA), and the Burden Augmented by Deadliness and Impact.^{34,35}

Recommendation: Make central in the framework varied and flexible valuation methods that synthesize the value from all the areas ICER currently recognizes, rather than as additional contextual criteria that have minimal impact on the ultimate assessment of value. ICER had previously attempted a modified MCDA and should secure learnings from that experience and expert input to inform alternative approaches to incorporate additional data in a robust manner, with relevant weights. This is an evolving field and an iterative approach may be needed which can be refined over time. Until best practices are identified, emphasis should be placed on flexibility, enabling early patient preference and expert input to inform weighting, and ensuring full transparency around the process.

(iv) Uncertainty

Uncertainty is unavoidable and should be managed by incorporating all relevant data as part of the assessment and enabling more data collection over time without penalizing innovation from the start. This includes explicit methods that allow for the incorporation of real-world evidence (RWE) and other data beyond randomized, controlled trials (RCTs). Until more data are available, ICER should take extra caution when reporting results of scenario analyses and sensitivity analyses that are not comprehensive enough to address uncertainty but are communicated with results as absolutes and averages, without context or robust quantification of unknowns. There are examples where ICER used optimistic assumptions when little to no data was available (e.g., gene therapies, CAR-T) and we encourage ICER to continue to incentivize innovation in areas of high patient burden, when data is initially limited and over time becomes available.

Recommendation: ICER's value framework should incorporate all relevant data beyond RCT data, including real-world evidence (RWE) such as that derived from claims databases and electronic records. In addition,

patient-generated data should have equal weight to other types of data and every effort should be made to include local community patient data to ensure that the assessment is relevant to the patient community it is designed to serve. Adequate measures should be recommended to address the uncertainty in evidence in a manner that protects patient access, such as risk share agreements and innovative contracts. Results should be presented as ranges rather than absolutes to acknowledge the significant uncertainty associated with these assessments. Reports should state how the results may differ under scenarios where patients respond differentially to alternative treatment options and value the various outcomes accordingly.

(v) Broad Societal or Multiple Perspectives

ICER should incorporate patient, caregiver, and employer costs in its 2020 Framework, and reflect costs incurred by wider society in its value assessments. ICER's current framework employs the perspective of the payer/healthcare system not the wider population. Limiting costs to those incurred by payers and the healthcare system will lead to decisions that shift costs to patients, their caregivers, employers, and wider society. By modifying this to reflect wider society, or at least including multiple perspectives as opposed to the payer/healthcare system perspective as the base-case, the results will have greater accountability to the impact of costs on wider society including patient out-of-pocket costs, employer costs and productivity losses.

In ICER's current approach, costs are not 'saved' but simply shifted away from the payer; ICER has the opportunity to present broader savings for society. Specific patient groups, their caregivers and employers are likely to be penalized because of this choice of perspective. For example, depression is a disease that the World Health Organization reports as the largest single cause of global burden of illness and more than half of costs are from lost productivity; this cost burden is similar for pain.^{36,37} In autism spectrum disorders, 90% of lifetime costs are borne by patients, their caregivers, and society, with patient out-of-pocket costs three times greater than direct healthcare costs.³⁸ High costs outside of the medical system are not limited to a few indications. In a recent systematic review of high-cost drugs, non-medical costs on average comprised 45% of total costs and their inclusion materially changed decision-making in 31% of cases.³⁹ These are conditions affecting patients and caregivers who cannot easily advocate for themselves and are affected by cost burdens that would be silent in ICER's approach to measuring cost. Exclusion of these costs in assessing the value of new health interventions puts a significant burden not only on patients and their caregivers, but also on employers. Self-insured employers represent 91% of people working in companies above 5,000 employees.⁴⁰

By adopting a broad societal perspective, ICER's choice of perspective will better align with over 20 years of expert input. The First Panel on Cost-effectiveness in Health and Medicine convened by the US Public Health Service (PHS) recommended using a societal perspective as the reference case.⁴¹ The panel, made up of leading experts in medicine, health economics and health technology assessment, recommended capturing all costs from the perspective of society over 20 years ago as best practice.⁴² This was confirmed in the Second Panel on Cost-effectiveness in Health and Medicine in 2016.⁴³

Recommendation: Payer-borne direct monetary costs are only one aspect of healthcare burden. ICER should include costs and cost savings resulting from treatment that are relevant to all stakeholders, including non-

medical costs, such as patient and caregiver out-of-pocket costs and lost productivity costs in its 2020 Framework reference case as is recommended by the Panel on Cost-effectiveness in Health and Medicine.

3. ADAPTATIONS/SPECIAL CONSIDERATIONS

(i) Rare Disease & Special Considerations

ICER's Framework should make special provisions for patients with rare disease and other special populations, as it has done for patients with ultra-rare conditions. Although ICER has made advances to allow special considerations for ultra-rare conditions, the current framework runs counter to the US Orphan Drug Act (ODA) of 1983, the legislation designed to incentivize innovation and protect all patients with rare diseases (not just those with ultra-rare conditions).⁴⁴ By limiting special considerations to those conditions with a prevalence of 10,000 or less (*i.e.*, ultra-rare), ICER's current framework arbitrarily puts all other rare diseases with a prevalence of 10,001 or more into the same category as common illnesses, with the same evidence requirements and value assessment criteria. This ignores the magnitude of difficulty in performing clinical trials and collecting real-world evidence for rare diseases that do not meet the criteria for ultra-rare disease. The current framework also excludes the costs incurred by patients, caregivers, employers and society, undervaluing the ability of new treatments to offset the significant burden of both rare and ultra-rare disease. The framework's application of the QALY presents several very specific challenges, excluding these patients from an equal chance at health, or a healthy life and devaluing rare disease patients who have a limited life expectancy. In addition, the choice to use static cost-effectiveness thresholds is not informed by preferences of US citizens or the government. This unfortunate categorization will essentially lead to most (if not all) interventions for these rare disease patients (with disease prevalence >10,000) receiving a 'low' value rating, without proper appraisal. This will likely have consequences in slowing the pace of scientific innovation necessary to prolong survival, improve quality of life, and potentially find cures for patients with all rare diseases.

Recommendation: ICER should include special framework adaptations for all rare (orphan) diseases, not just ultra-rare diseases. We encourage ICER not to apply the same value framework to orphan drugs as for common drugs as the methodological concerns around common diseases would be further amplified in orphan diseases, and not to attempt to set a national threshold for orphan drugs. ICER's 2020 Framework should align with the definitions and provisions in place to protect patients with rare diseases, including provisions that account for the difficulty in designing, recruiting, and performing clinical studies. ICER should ensure the patient voice is heard and put at the center of assessments and should include costs relevant to both them and wider society.

(ii) Biosimilars

The introduction of a biosimilar marks a significant milestone in the treatment landscape, providing more options for patients, and all available biosimilars should be included in value assessments, including those conducted by ICER. Biosimilars present the opportunity for greater value for biologic medicines and greater savings potential that will contribute to the sustainability of the healthcare system.

A biosimilar is not a new category of medicine but an FDA-approved molecule deemed highly similar to a prior approved biologic medicine and should not be treated as a separate class in value assessments.

Highly similar is defined by the FDA as having no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) when compared to an existing FDA-approved reference product.⁴⁵ The totality of evidence, including analytical, non-clinical, and clinical data is the basis of the FDA assessment of the biosimilarity of a drug and of the marketing authorization in all approved indications of the reference product, including those in which the biosimilar has not been studied in a phase 3 clinical study. To be consistent with this, it is important not to create the perception that these are a separate category.

In the US marketplace, biosimilar medicines compete directly with the biosimilar's reference product, and other products approved as biosimilar to that reference product. A biosimilar product may be approved only to treat conditions for which its reference product is already licensed and intended to be used. For these reasons, instead of creating a separate biosimilars category (such as "Exemplar Biosimilars"), ICER's analysis should treat biosimilars in the same manner as the reference products, just as they compete directly against the reference products on a level-playing-field basis in the marketplace. In keeping with this, ICER's ongoing Rheumatoid Arthritis Condition Update for example, should include *all* available biosimilars, including Renflexis® in addition to Inflectra®.⁴⁶ With this approach, ICER has the opportunity to help accelerate patient treatment with all biologics, not just a limited few. Equally, this is aligned with precedents in how ICER has considered biosimilars in prior assessments and updates.

Recommendation: ICER should employ a consistent approach to biosimilars as with prior assessments and include all available FDA-approved biosimilars in the assessment and avoid introducing it as a new category.

CONCLUSIONS

Amgen appreciates ICER's engagement of stakeholders in an effort to continuously update its Framework. We urge ICER to modify the current framework based on these recommendations, which are founded in guiding principles representing best practice and rigorous scientific methods. ICER has an opportunity to take a longer-term view of its role and command greater credibility by defining its role as one that *offers guidance and informs decisions* with a systematic approach to the evaluation of evidence with flexibility, inclusiveness, scientific integrity, transparency, and patient centricity, in the absence of absolutes based on subjective thresholds. Taking this direction will allow ICER to become a more trusted independent organization. Budget holders and decision makers can benefit if ICER focuses on key pillars of evidence, robust analytics, and the identification of areas of uncertainty. This ultimately allows the budget holders and decision makers to leverage ICER's insights in making their decisions on value. Thoughtful attention should be given to the fact that at any given time we are all patients who will likely feel the impact of ICER's assessments. These assessments could have far reaching and unintended human costs and implications for all of us.

REFERENCES

- ¹ ICER. What is ICER. [Link](#)
- ² Sullivan SD, Watkins J, Sweet B, Ramsey SD. Health technology assessment in health-care decisions in the United States. *Value in Health*. 2009 Jun 1;12:S39-44. [Link](#)
- ³ UK Parliament. Commons Select Committee. National Institute for Health and Clinical Excellence (NICE). [Link](#)
- ⁴ UK Parliament. Early day motion 2766. National Institute for Health and Clinical Excellence (NICE) Decision on Alzheimer's drugs. 17.10.2006. [Link](#)
- ⁵ UK Parliament. Early day motion 1707 NICE and age-related macular degeneration. 14.06.2007. [Link](#)
- ⁶ Drug watchdog NICE 'spends more on 'spin' than tests on new treatments'. Mail Online. [Link](#)
- ⁷ Johnston L. Health watchdog NICE told to 'clean up its act' after statins scandal. *The Sunday Express*. Sun, Jun 29, 2014. [Link](#)
- ⁸ This is based on an analysis in May 2019 on ICER's 3 voting panels (CTAF, New England CEPAC, and Midwest CEPAC) that classified members by their field of expertise.
- ICER: Institute for Clinical and Economic Review. New England CEPAC Voting Body. May 15, 2019. [Link](#)
- ICER: Institute for Clinical and Economic Review. Midwest CEPAC Voting Body. May 15, 2019. [Link](#)
- ICER: Institute for Clinical and Economic Review. CTAF Voting Body. May 15, 2019. [Link](#)
- *Members who were academics and physicians were counted as academics.
- ⁹ ICON. Industry Perceptions and Expectations: The role of ICER as an Independent HTA. [Link](#)
- ¹⁰ Xcenda. Applying Cost-Effectiveness Thresholds to the Real World: Implications on Access for Medicare Beneficiaries. Issue Brief. May 30, 2018. [Link](#)
- ¹¹ Thompson R, Vaidya S, Teynor M. The utility of different approaches to developing health utilities data in childhood rare diseases – a case study in spinal muscular atrophy (SMA). *Value in Health*. 2017; 20: A399-A811. [Link](#)
- ¹² Tim Wilsdon, Amy Serota. Charles River Associates. A comparative analysis of the role and impact of Health Technology Assessment. May 2011.
- ¹³ O'Donnell JC, Pham SV, Pashos CL, Miller DW, Smith MD. Health technology assessment: lessons learned from around the world—an overview. *Value in Health*. 2009 Jun;12:S1-5.
- ¹⁴ "For countries where HTA assessment plays a role in formal pricing and reimbursement processes (e.g. France, Netherlands, Sweden) this measure gives an indication of the delay to market access imposed by HTA (although this could also be due to other factors). However, for countries where HTA is not part of the pricing and reimbursement process and takes place after product launch (e.g. UK, Germany), the measure does not capture the impact of HTA on the speed at which medicines are available." Patients WAIT Indicator 2010, EFPIA
- ¹⁵ Mason et al. Comparison of anticancer drug coverage decisions in the US and UK: does the evidence support the rhetoric? *Journal of Clinical Oncology*, July 2010.
- ¹⁶ Bending MW, Hutton J, McGrath C, "Comparative-effectiveness versus cost-effectiveness: A comparison of the French and Scottish approaches to Single Technology Appraisal", Monday May 17th 2010, ISPOR International, USA
- ¹⁷ Access to innovative treatments in rheumatoid arthritis in Europe", report prepared for EFPIA, October 2009
- ¹⁸ ISPOR. ISPOR Special Task Force Provides Recommendations for Measuring and Communicating the Value of Pharmaceuticals and Other Technologies in the US, February 26, 2018. [Link](#)
- ¹⁹ Pettitt DA, Raza S, Naughton B, Roscoe A, Ramakrishnan A, Ali A, Davies B, Dopson S, Hollander G, Smith JA, Brindley DA. The limitations of QALY: a literature review. *Journal of Stem Cell Research and Therapy*. 2016 Jan 1;6(4). [Link](#)
- ²⁰ *Op. Cit.*, Pettitt et al., 2016. [Link](#)
- ²¹ IMS. Impact of cost-per-QALY reimbursement criteria on access to cancer drugs. IMS Institute for Healthcare Informatics. Dec. 2014.
- ²² Robinson LA, Hammitt JK, Chang AY, Resch S. Understanding and improving the one and three times GDP per capita cost-effectiveness thresholds. *Health Policy and Planning*. 2016 Jul 24;czw096. [Link](#)
- ²³ Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. *Bulletin of the World Health Organization*. 2015 Feb;93(2):118-24. [Link](#)
- ²⁴ Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, Devlin N, Smith PC, Sculpher M. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health technology assessment*. 2015;1-542. [Link](#)
- ²⁵ Claxton, K., Martin, S., Soares, M., Rice, N., Spackman, E., Hinde, S., Devlin, N., Smith, P.C. and Sculpher, M. (2013) Methods for the estimation of the NICE cost effectiveness threshold. CHE Research Paper 81. Revised following referees' comments. York: Centre for Health Economics, University of York. 2013. [Link](#)
- ²⁶ Barnsley P, Towse A, Sussex J. Critique of CHE research paper 81: methods for the estimation of the NICE cost effectiveness threshold. 2013. [Link](#)
- ²⁷ Demonstrating the inappropriateness of this lower threshold, in 2009, US researchers derived a QALY range for kidney dialysis averaging \$129,090 per QALY with a top range of \$488,360 for sicker patients. In the ensuing 8-10 years since this analysis, the QALY range is likely to be even higher. Lee CP, Chertow GM, Zenios SA. An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. *Value in Health*. 2009 Jan 1;12(1):80-7. [Link](#)
- ²⁸ Another 2008 study that derived a US QALY threshold empirically from researchers at Yale calculates a range of \$118,000 to \$264,000 cost per QALY: this upper range is likely more appropriate for the US, as it represents patients that are insured. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the \$50,000 per quality-adjusted life-year decision rule? *Med Care* 2008;46:349-356

Amgen Comments for ICER's 2020 Value Assessment Framework

- ²⁹ Thung SF, Funai EF, Grobman WA. The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. *American journal of obstetrics and gynecology*. 2009 Mar 31;200(3):267-e1.
- ³⁰ Gandra SR, Villa G, Fonarow GC, Lothgren M, Lindgren P, Somaratne R, van Hout B. Cost-Effectiveness of LDL-C Lowering With Evolocumab in Patients With High Cardiovascular Risk in the United States. *Clinical cardiology*. 2016 Jun 1;39(6):313-20. [Link](#)
- ³¹ Sabatine MS, Guigliano RP, Keech AC, *et al*. Evolocumab and clinical outcomes in patients with cardiovascular disease. *New Engl J Med* 2017; 376: 1713-1722.
- ³² Greenberg D, Earle C, Fang CH, Eldar-Lissai A, Neumann PJ. When is cancer care cost-effective? A systematic overview of cost-utility analyses in oncology. *Journal of the National Cancer Institute*. 2010 Jan 20;102(2):82-8. [Link](#)
- ³³ Aggarwal S, Topaloglu H. Systematic review of cost-effectiveness analyses of ultra-orphan therapies. *Value in Health*. 2016 May 1;19(3):A247. [Link](#)
- ³⁴ Jit M. MCDA from a health economics perspective: opportunities and pitfalls of extending economic evaluation to incorporate broader outcomes. *Cost Effectiveness and Resource Allocation*. 2018 Nov;16(1):45. [Link](#)
- ³⁵ Caro J. Novel Approaches to Value Assessment, Beyond Cost-Effectiveness Framework. 2018. [Link](#)
- ³⁶ Krol M, Papenburg J, Koopmanschap M, Brouwer W. Do productivity costs matter? The impact of including productivity costs on the incremental costs of interventions targeted at depressive disorders. *Pharmacoeconomics*. 2011;29:601–619.
- ³⁷ Gaskin D, Richard P. Appendix C: the economic costs of pain in the United States. *Relieving pain in America: a blueprint for transforming prevention, care, education, and research*. [Link](#)
- ³⁸ Ganz ML. The lifetime distribution of the incremental societal costs of autism. *Archives of pediatrics & adolescent medicine*. 2007 Apr 1;161(4):343-9. [Link](#)
- ³⁹ Krol M, Papenburg J, Tan SS, Brouwer W, Hakkaart L. A noticeable difference? Productivity costs related to paid and unpaid work in economic evaluations on expensive drugs. *The European Journal of Health Economics*. 2016;17:391-402. doi:10.1007/s10198-015-0685-x. [Link](#)
- ⁴⁰ Herman B. Self-service insurance: Insurers forced to compete harder for self-insured customers. *Modern Healthcare*. January 3, 2015. [Link](#)
- ⁴¹ Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *Jama*. 1996 Oct 16;276(15):1253-8. [Link](#)
- ⁴² Weinstein *et al*. 1996 state that “The major categories of resource use that should be included are costs of health care services; costs of patient time expended for the intervention; costs associated with caregiving (paid or unpaid); other costs associated with illness, such as child care and travel expenses; economic costs borne by employers, other employees, and the rest of society, including so-called friction costs associated with absenteeism and employee turnover; and costs associated with nonhealth impacts of the intervention, such as on the educational system, the criminal justice system, or the environment.”
- ⁴³ *Cost-Effectiveness in Health and Medicine*. Edited by Newmann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Oxford University Press, New York 2017. [Link](#)
- ⁴⁴ Global Genes, Allies in Rare Disease. (2015). RARE Diseases: Facts and Statistics. [Link](#)
- ⁴⁵ FDA. Biosimilar Development, Review, and Approval. [Link](#)
- ⁴⁶ FDA Biosimilar Product Information. [Link](#)

June 10, 2019

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

Dear Dr. Pearson:

On behalf of the more than 54 million Americans and 300,000 children with doctor-diagnosed arthritis in the United States, the Arthritis Foundation is pleased to comment on the Institute for Clinical and Economic Review's (ICER) solicitation for feedback on the 2020 Value Assessment Framework. The Arthritis Foundation is the nation's premier organization focused on helping people with arthritis conquer everyday battles through life-changing information and resources, access to optimal care, advancements in science, and community connections.

The Arthritis Foundation signed on to the letter submitted by the Partnership to Improve Patient Care and we endorse the recommendations provided there. We share ICER's goal to achieve sustainable access to high-value treatments and care for all patients; specific to our community, we are also providing additional points for your consideration below.

Short- and Long-Term Perspectives

With regard to the tension between short-term budgeting and long-term perspectives on value assessment, we urge ICER to continue to push for a clearer compromise between these positions. While an important consideration that insurers and decision-makers "currently operate within" a short-term budget construct, viewing this as an immovable or unchangeable reality seems to prevent any opportunity to innovate value assessment. Within rheumatologic and musculoskeletal conditions, which are almost always lifelong, there is no such thing as a short-term perspective. Rather, missed opportunities early in disease course, whether due to lack of effective therapy, access challenges, or other barriers, result in significant cost increases downstream. ICER is in a unique position, as a neutral convener of multiple stakeholders, to tangibly address this disconnect, and finally revamp the current process, which ultimately obfuscates longer term patient, system, and societal costs, in its focus on short term economies.

Patient Engagement

For all of ICER's efforts, we continue to offer access to the insights and patient-generated data from our Arthritis Foundation community. The Arthritis Foundation recently aligned its 70-year-old patient network under the Live Yes Arthritis Network model. This facilitates peer-to-peer connections both in-person and online in order to empower people with arthritis to live their best life. A key component of this network is the generation of real-time Patient Reported Outcomes (PROs) that will shape the future of arthritis care and treatment. Our goals for these PROs are threefold: allow patients to better understand their health over time; enable the Arthritis Foundation to tailor programming to specific market needs; and help researchers and policymakers understand patient health trends in order to improve population health. For instance, in 2017 the Arthritis Foundation presented patient-centered research at ICER's review of the evidence for treatments of rheumatoid arthritis (RA). Among the key findings were the observations from the Live Yes Arthritis Network that strongly reinforce the notion that many or most RA patients:

- Cycle over several medications throughout the course of their disease
- Change medications early in their disease treatment
- Must overcome significant systemic barriers in order to receive doctor-prescribed medications
- Often receive more medications for pain and depression, and therefore accrue additional costs to the health care system, when their RA is not well controlled

Other insights from our previously-submitted data include:

- ICER should continue to expand the vehicles for incorporating patient input to more fully understand and infuse patient feedback. This includes better outreach at the front end to ensure patients are truly aware of the opportunity.
- In addition to the importance of including patients is the importance of doing so in a meaningful way. In the Draft Evidence Report, the changes that have been made based on patient and other input are highlighted, however it would be useful to note changes made based on patient and other input throughout all phases of review. Further, it would be valuable to highlight areas where patient input was collected but did not change the end result, and why that was the case.
- If comments from a patient are not fully understood, there must be a mechanism to reach back to the submitter to clarify what he or she meant. We encourage continued efforts to establish greater dialogue with patients up front, versus waiting until the public meeting.
- Facilitating travel for patients to attend in-person meetings is critical. Without assistance, only patients with financial resources will be able to attend and the discussion will lack a critical voice, particularly within the context of a cost conversation.

Patient Perspective Value Framework

Finally, we strongly recommend that ICER consult with and rely on Avalere and FasterCure's Patient Perspective Value Framework (PPVF) and the stakeholders involved in that work, including the Arthritis Foundation. The PPVF endeavors to reach truly equitable value

assessment results through careful consideration of the perspectives of each and every stakeholder, and weighting elements and perspectives accordingly. One recommendation, for instance, is that there is a lack of routine collection of patient-centered data. Without consistent collection of this type of real-world evidence, it is more difficult to identify unmet needs of patients during the treatment decision-making process. Another approach is the development of validated shared decision-making tools that include processes for collection of patient preferences and other patient centered outcomes data. The latest recommendations can be found [online](#) and we encourage ICER to integrate these types of patient perspectives and tools into the value framework.¹

The Arthritis Foundation appreciates the opportunity to comment on ICER's initiative. We strongly encourage the updated framework to further emphasize the importance of increasing patient centricity in value assessment. Please contact us with questions or for more information.

¹ Avalere. (2019). "Avalere Releases Recommendations to Drive More Patient Orientation in Value Assessment Methodology." <https://avalere.com/insights/avalere-releases-recommendations-to-drive-more-patient-orientation-in-value-assessment-methodology>



June 7, 2019

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

Dear Dr. Pearson:

The Asthma and Allergy Foundation of America (“AAFA”) thanks the Institute for Clinical and Economic Review (“ICER”) for the opportunity to comment as ICER launches the 2020 Value Assessment Update Process.

Overall, AAFA appreciates the work that ICER does, and particularly the willingness to meaningfully engage with patient perspectives. As we have noted most recently in comments to ICER on biologic treatments for asthma and on peanut allergy treatment, AAFA believes that thoughtful inclusion of patient experience data is essential to accurately reflect the true impact, and therefore “worth,” of new and evolving treatments. We look forward to reviewing the draft revisions to the framework later this year, and in the meantime offer the following general comments regarding ICER’s approach:

Modified Social Perspective: We urge ICER to include the modified societal perspective as part of the base analysis to more accurately reflect patient perspective. As noted in our letter on peanut allergy treatment, solely focusing on direct medical costs for the base case analysis with a modified societal perspective in the sensitivity analysis seriously misrepresents the value of a treatment for any food allergy. In the case of food allergy, families have consistently reported that food allergy significantly impacts meal preparation and social activities. While we understand that the direct medical costs are of interests to many stakeholders (payers, in particular) and should be explicitly reported, the Second Panel on Cost Effectiveness recommends that economic models should report both perspectives (societal and health sector) and produce an impact inventory to aid in decision making.

Customized Data Sets: ICER analyses typically rely on epidemiologic data to estimate potential patient populations for specific products. As argued in our letter on biologic treatment for asthma, when available, real-world healthcare data should be used to estimate the potential patient population and treatment effectiveness. Claims and enrollment data sets, such as the US data sets prepared by CMS, IBM (formerly Truven), and HCCI, are available to researchers for use—often with a year or less of reporting lag. Such data sets have been underutilized for answering critical asthma disease and treatment questions.

Sensitivity analyses: When appropriate, we encourage ICER to run sensitivity analyses using multiple scenarios. As noted in our asthma letter, we found that when we combined variables to assess a range of scenarios, relatively modest changes in ICER’s cost and utility assumptions had a significant impact on cost per QALY.



Caregiver Burden: We know from our food allergy community that food allergies uniquely affect a whole family. In fact, nearly every health condition has an impact on family and caregivers. As we noted in the peanut allergy treatment letter, that analysis appeared to reflect potential diminished burden on caregivers, but not potential quality of life gains attributed to the caregiver, possibly underestimating the true societal value of treatment. We encourage ICER to fully reflect caregiver burden and potential benefits of interventions for caregivers in future analyses.

Thank you very much for your time and attention. We look forward to continuing to work with ICER to incorporate the patient and family perspective in your analyses.

Sincerely,

Kenneth Mendez,
President and Chief Executive Officer
Asthma and Allergy Foundation of America

June 10, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: ICER 2020 Value Assessment Framework Open Input

Dear Dr. Pearson,

Bayer Pharmaceuticals (“Bayer”) appreciates the opportunity to submit these comments on the Institute of Clinical and Economic Review’s (ICER) 2020 Value Assessment Framework update.

Bayer is an enterprise with core competencies in the Life Sciences fields of health care and agriculture with nearly 25,000 employees in 300 sites across the United States. Our products and services are designed to benefit people and improve their quality of life. At the same time, we aim to create value through innovation and are committed to the principles of sustainable development and to our social and ethical responsibilities as a corporate citizen.

We commend ICER for continually striving to improve their approach to assessing therapies to ensure the most robust and balanced reviews. We welcome the opportunity to share with ICER our experiences in an effort to further enhance the ICER process. In that spirit, we would like to offer our recommendations in this letter. Our comments below are organized to address the topics outlined in the project announcement.

Methods to evaluate therapies for ultra-rare diseases (URDs):

Innovative Oncology Treatment Evaluations: Bayer has a long-standing commitment to cancer research, with dedication to be at the forefront of the next wave of innovative oncology treatments. The discovery of specific targetable genomic alterations has led the shift from identification of targets as part of scientific research to use by healthcare providers in daily clinical practice. This has begun a transition from a “one-size-fits-all” approach of categorizing cancers by histology alone to a treatment focus on the specific genetic alterations (tissue-agnostic) (ACS 2018, Yates 2018). Advances in genomic testing have significantly evolved over the past several years, becoming both quicker and less costly—thus allowing more patients to benefit from the results of this testing (Jarvis 2017, Horak 2016). Epidemiologic estimation for specific genomic alterations in cancer has continued to grow and is becoming more robust over time. For example, *neurotrophic tyrosine receptor kinase (NTRK)* gene fusions drive tumorigenesis in a small fraction of many tumors, regardless of tissue type (Stransky 2014). *NTRK* gene fusions have been reported across a multitude of malignancies in pediatric and adults, ranging from <1% to 3% in common cancer types (such as lung cancers and colorectal cancer) to almost 100% in rare tumor types (such as mammary analogue secretory carcinoma and infantile fibrosarcoma) (Appendix, Table 1). It is currently estimated that the prevalence of

NTRK gene fusions across all tumors is between 1,500 to 5,000 patients in the United States (US) each year (Hyman 2017).

ICER's 2017 update to its VAF methodology URDs applies to therapies that, based on approved indications and planned clinical trials, will be eligible to treat no more than 10,000 US patients (ICER 2017). When considering tumor incidence alone, many common tumor types (eg, lung cancer and colorectal cancer,) do not meet criteria for evaluation under ICER's modified value assessment framework for ultra-rare diseases. However, when considering epidemiological estimates of the frequency of specific genomic alterations within individual tumor types, it is apparent that incidence rates fall well under 10,000 patients. For example, Table 2 (Appendix) lists the incidence of common and rare tumor types within the US population, as well as the incidence of *NTRK* gene fusion frequencies for respective tumor types within the same population. Therapies that target specific, rare genomic alterations have, virtually by definition, a very limited patient population. Methodologies and frameworks, including ICER's, have not yet matured sufficiently to address the more complex aspects of valuing targeted therapies or incorporating evidence from studies that are driven by genetic markers rather than tumor type. As such, ICER should apply methodology consistent with the modified VAF for URDs to the evaluation of targeted therapies.

Recommendations:

- ICER should consider *all* epidemiological evidence available when estimating the size of the target patient population in determining the value of treatments. This includes incidence rates of specific genomic alterations, which may limit the number of patients eligible to receive certain treatments and impact the selection of appropriate methods.
- ICER should apply the modified VAF methodology for URDs to the evaluation of all treatments intended for a small treatment-eligible patient population (ie, less than 10,000 patients), irrespective of how this may be defined (eg, targeted treatments for specific genomic alterations, low incidence conditions, lines of therapy, narrow definition of treatment eligible population) and consistent with the corresponding epidemiologic evidence. This consideration is extremely important when determining the value of innovative new therapies in areas such as in oncology which may rely on genomics, biomarkers, or other criteria to target patient therapies.

Broader Cost per QALY Range for URDs: ICER has also adapted its VAF to provide cost-effectiveness results for the broader range of \$50,000-\$500,000 per quality-adjusted life year (QALY) gained for treatments of URDs (ICER 2017). Panel voting on the long-term value for money of treatments may be impacted by this broader range of cost-effectiveness. ICER has noted that value-based price benchmarks using the standard range of \$100,000-\$150,000 per QALY will still be used for URDs, but ICER will indicate in all reports that decision-makers often give special weight to additional benefits and contextual considerations when determining coverage of more expensive treatments for ultra-rare diseases (ICER 2017).

- Recommendations:

- Bayer agrees with applying the broader range of \$50,000-\$500,000 per QALY

utilized by ICER to determine the cost-effectiveness of treatments for URDs and encourages ICER to apply this range consistently to all interventions for which the treatment eligible population is less than 10,000 patients irrespective of the broader diagnosis code or category.

- Relative to the willingness to pay (WTP) boundary currently utilized for ultra-rare diseases, the upper WTP boundary should increase as the target patient population size decreases when estimating the cost-effectiveness of therapies (ie, higher upper WTP boundary for target patient population size of 1,000 patients compared to the upper WTP boundary for target patient population size of 10,000 patients) in order to capture the magnitude of the benefit.
- Further, ICER should extend the upper WTP boundary used to estimate the value-based prices of treatments with small targeted patient populations to align with those utilized in cost-effectiveness analyses (ie, \$50,000-\$500,000 per QALY).

Economic models and transparency:

Consideration of Value-Based Contracts: Since ICER's VAF update in 2017, the US health care system has continued to shift towards payments based on value rather than volume. Value-based contracts (VBC) have continued to gain popularity to tie payment to objective outcome measures as a means of demonstrating effectiveness and reducing risk for payers, providing improved access to medications, generating real-world evidence, and proposing alternative pricing mechanisms (Drozd 2018, NPC). Some VBCs include a full money-back guarantee for patients who do not respond to therapy, or those patients who do not demonstrate or achieve pre-specified outcomes. In a 2018 survey, VBCs were reported to provide cost-savings in 74% of health plans (Drozd 2018). Another study showed patients enrolled in health plans with VBCs have about 28% lower out-of-pocket costs compared to patients enrolled in health plans without VBCs (PhRMA 2018). With the success of VBCs to date, it is expected that implementation of these types of arrangements will continue to increase. ICER's 2017-2019 VAF methodology does not include any assumptions to account for alternate payment methodologies and the impact it will have on economic outcomes. As such, Bayer encourages ICER to formally incorporate methods that consider the full impact of VBCs in their assessment of value through the 2020 VAF update.

- **Recommendations:**

- ICER's cost-effectiveness analysis should consider potential cost implications of value-based contracts. The base case analysis, or at a minimum a scenario analysis, should be conducted to account for a lower cost, or no cost (ie, \$0), of treatment for non-responders if a value-based contract is in place for the therapy being evaluated. ICER's cost-effectiveness analysis should allow stakeholders to determine potential ranges of cost-savings through value-based contracts, and account for this consideration when determining the value of a therapy.
- In order to reflect any potential variability and uncertainty Bayer also encourages ICER to report ranges of potential outcomes for all analyses, and consequently value-based prices, rather than reporting point estimates. For example, we suggest presenting a range of predicted results that consider outcomes and costs of value-based contracts. This will provide a more accurate representation of the long-term value of therapies that ICER is evaluating.

Weight of QALY and evLYG in Evaluations: ICER has requested specific feedback related to the use of both the QALY and the Equal Value of Life Years Gained (evLYG) to evaluate the degree of improvement in health outcomes. The QALY remains the gold standard in cost-effectiveness analyses to capture both the impact of a treatment of a patient's length of life and also the impact on their health-related quality of life (Whitehead 2010). However, concerns raised regarding the undervaluing of treatments due to the use of the QALY has resulted in ICER incorporating a calculation of evLYG to measure any gains in length of life, regardless of the treatment's ability to improve patients' quality of life (ICER 2018). Although ICER currently reports both outcomes of cost per QALY and cost per evLYG in order to take a broader view of cost-effectiveness, ICER's 2017-2019 VAF methodology does not place equal emphasis on results of both measures of cost-effectiveness. Although ICER is including cost per evLYG cost-effectiveness results to supplement calculations of QALYs gained, the manner in which these results are presented in the 2017-2019 VAF reports does not convey the equal importance of this information in determining value.

- Recommendations:
 - ICER should allocate equal weight to both cost per QALY and cost per evLYG in evaluations. Base case results, threshold analyses, as well as scenario analyses should include estimated cost-effectiveness ratios for both cost per QALY and cost per evLYG. This will allow stakeholders to understand and efficiently utilize all estimates cost-effectiveness, including the calculation of evLYGs.

Valuing a Cure Comments: Bayer recently submitted comments to ICER during the open input period for ICER's Valuing a Cure project. Our comments relating to ICER's budget impact analysis should also be considered for the 2020 VAF update. Determining the short-term affordability (ie, budget impact) of any intervention is essential to fiscal responsibility. Budget impact takes into account, by definition, the most immediate financial impact to the budget holder (over a period of up to 5 years), while the benefits of a treatment, may only be realized over a much longer time period (Sullivan 2014). Evaluation of short-term affordability, and the resulting value-based price, must account not only for variation in the modeling parameters, but for potential variability in ICER's estimate of the annual budget impact threshold that may be reflective of value-based contracts.

- Recommendations:
 - ICER's budget impact analysis should consider the impact of varying payment options for treatments, including value-based contracts.
 - To address potential variation in estimates of short-term affordability, Bayer recommends that ICER should estimate a reasonable range of potential annual budget impact thresholds by varying the underlying estimates used to determine the annual threshold.
 - Further, ICER should estimate the budget impact threshold for a 5-year period based on historical data inputs to provide a benchmark which applies to a longer time horizon and accounts for year-to-year variation in the annual estimates of GDP, health care spending, and new molecular entities entering the market.
 - In addition, any real-world evidence gathered from value-based contracts should be considered as part of ICER's evaluations and evidence updates.

Non-clinical benefits and contextual considerations:

Patient-Centric Considerations: We are moving into an era of patient-centric healthcare. Studies have demonstrated better outcomes (ie, lower readmission rates, better adherence, and fewer delays in care) at lower costs for well-informed patients who are involved in shared decision making regarding their treatment and care options. Although ICER claims to take a societal perspective in its current VAF methodology, ICER has repeatedly received comments from stakeholders requesting ICER to take a more patient-centric approach in its 2017-2019 VAF methodology. ICER should provide increased consideration to the incorporation of patient perspective in its methodology. ICER includes multiple formal and informal opportunities for patients, caregivers, and patient advocacy group to engage with ICER and provide feedback. However, it remains unclear how ICER incorporates patient feedback and the extent to which ICER actually takes into account the patient perspective when determining the value of a therapy. As shared decision making becomes increasingly commonplace, it is important for ICER to consider the patient perspective when determining the value of a therapy. Patients and providers should be able to utilize ICER final evaluations in a meaningful manner to help guide shared decision making about the value of therapies that ICER evaluates.

- Recommendations:
 - The patient perspective (including, but not defined by patient reported outcomes) should be elevated in importance and visibility in ICER's evidence reports. It is Bayer's recommendation that ICER add a section to the evidence reports specifically on Patient Perspectives that aligns with the current sections on comparative clinical effectiveness, cost-effectiveness, and so forth.
 - ICER's final reports, including the final evaluation summary, should be improved to be more user-friendly with lay-language that clearly outlines how ICER considered the patient perspective and that would allow patients of all backgrounds to understand ICER's conclusions regarding value of treatments.
 - Elements of value, such as those captured by ICER in the other benefits and contextual considerations section of the report, should be summarized in a table or graphic side-by-side with the comparative effectiveness, long-term value, and short-term affordability estimates as part of the Report-at-a-Glance. This would allow readers to readily view and interpret key determinants of value of an intervention as a whole rather than separately. Any summaries must be inclusive of the full range of values estimated under varying assumptions to ensure full transparency of the uncertainty underlying them.

Evaluation of Digital Technologies: The era of patient-centric healthcare includes increased involvement of the patient in their own care pathways and treatments through the use of digital health technologies. The spectrum of digital therapeutics includes digital services (ie, those that support or improve patient behavior are independent of pharmaceutical intervention), adjunctive digital therapies (ie, those that add value to pharmaceutical treatments by improving clinical benefit), and drug replacement digital therapies (ie, those that offer direct clinical benefit and can therefore be used as standalone therapy) (Simon Kucher and Partners 2018). The FDA approves and regulates digital health technologies that make a claim for clinical benefit and/or safety. The FDA's Digital Health Innovation (DHI) Action Plan outlines efforts to ensure patients have timely access to high-quality, safe and effective digital health technologies (FDA 2019). Studies have shown that payers recognize the impact that digital health technologies can have on clinical

and economic outcomes, but are still often unwilling to cover the digital health technology (Walters 2016). ICER can help to bridge this chasm by conveying the value of digital health technologies through VAF assessments. ICER should consider the impact of digital health technologies as stand-alone therapies, as well as the impact of using digital health technologies to augment pharmaceutical treatments. It would be interesting to evaluate how the outcomes are affected by the use of digital health technologies, compared to the use of traditional pharmaceutical therapies alone.

- Recommendations:
 - ICER should develop a modified VAF methodology to evaluate the clinical, economic, and patient-centric outcomes of digital health technologies. This modified framework may include an expanded literature review that is inclusive of efficacy and economic outcomes of digital health technologies.
 - ICER should carry-out evaluations inclusive of scenario analyses of cost-effectiveness models that consider therapies that utilize digital health technologies to determine any potential long-term benefits.
 - ICER should seek to evaluate at least 1 digital health technology in calendar years 2020-2021.

Respectfully,

Todd Williamson

Vice President, Data Generation & Observational Studies

Bayer HealthCare Pharmaceuticals Inc.

References:

- American Cancer Society. How Is Chemotherapy Used to Treat Cancer? <https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/how-is-chemotherapy-used-to-treat-cancer.html>. Accessed May 23, 2019.
- Drozdz M. Pharmaceutical Research and Manufacturers of America (PhRMA). Number of value-based contracts continues to rise. August 27, 2018. <https://catalyst.phrma.org/number-of-value-based-contracts-continues-to-rise>. Accessed May 16, 2019.
- Federal Drug Administration. Digital Health Innovation Action Plan. March 22, 2019. <https://www.fda.gov/media/106331/download>. Accessed May 15, 2019.
- Horak P, Fröhling S, Glimm H. Integrating next-generation sequencing into clinical oncology: strategies, promises and pitfalls. *ESMO Open*. 2016 Nov 18;1(5):e000094.
- Hyman DM, et al. The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers. Presentation presented at: American Society of Oncology (ASCO) 2017 Annual Meeting. Chicago, Illinois; (Abstract #LBA2501).
- Institute for Clinical and Economic Review (ICER). Modifications to the ICER value assessment framework for treatments of ultra-rare diseases. November 2017. <https://icer-review.org/material/final-ultra-rare-adaptations/>. Accessed May 16, 2019.
- Institute for Clinical and Economic Review (ICER). The QALY: rewarding the care that most improves patients' lives. December 2018. https://icer-review.org/wp-content/uploads/2018/12/QALY_evLYG_FINAL.pdf. Accessed May 16, 2019.
- Jarvis LM. Cancer, redefined. *Chemical & Engineering News*. 2017;95(27):26-30.
- National Pharmaceutical Council (NPC). Value-based contracts. <https://www.npcnow.org/issues/access/provider-reimbursement/risk-sharing-agreements>. Accessed May 15, 2019.
- Pharmaceutical Research and Manufacturers of America (PhRMA). Delivering results for patients: the value of value-based contracts. February 2018. <http://phrma-docs.phrma.org/files/dmfile/PhRMA-Value-of-Value-Based-Contracts1.pdf>. Accessed May 16, 2019.
- Simon Kucher and Partners. Monetizing Digital Therapeutics. July 16, 2018. <https://www.simon-kucher.com/en/blog/monetizing-digital-therapeutics>. Accessed May 15, 2019.
- Stransky N, Cerami E, Schalm S, Kim JL, Lengauer C. The landscape of kinase fusions in cancer. *Nat Commun*. 2014 Sep 10;5:4846.
- Sullivan SD, et al. Budget Impact Analysis – Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health*. 2014;17(1):5-14.
- Walters T, Parcher B, Campbell C, Shah M. Appraising the value of digital health technologies from the managed care perspective: insights for evidence assessment and reimbursement in the U.S. Poster presented at: AMCP's 28th Annual Meeting and Expo; April 19-22, 2016; San Francisco, CA. First Interactive Digital Poster.

Whitehead S, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull. 2010;96(1):5-21.

Yates LR, Seoane J, Le Tourneau C, et al. The European Society for Medical Oncology (ESMO) Precision Medicine Glossary. Ann Oncol. 2018 Jan 1;29(1):30-35.

Appendix

Table 1. *NTRK* Gene Fusion Frequency Within Different Tumor Histologies

<5%	5%–25%	75%-100%
CNS <ul style="list-style-type: none"> • Astrocytoma¹ • Brain low-grade glioma² • Glioblastoma³ GI <ul style="list-style-type: none"> • CRC² • Cholangiocarcinoma⁴ Head and neck <ul style="list-style-type: none"> • Squamous cell carcinoma² Lung <ul style="list-style-type: none"> • Adenocarcinoma^{2,5} • Large cell neuroendocrine⁶ Other <ul style="list-style-type: none"> • Breast invasive carcinoma² • Melanoma² • Sarcoma² 	<ul style="list-style-type: none"> • Thyroid cancer: palliary⁷ • Pediatric high grade glioma⁸ • Spitz tumors⁹ • Pan-negative GIST¹⁰ 	<ul style="list-style-type: none"> • MASC of the salivary gland¹¹ • Secretory breast carcinoma¹² • IFS¹³ • Cellular subtype CMN^{14,15}

References: 1. Jones DT, et al. *Nat Genet.* 2013;45:927-934. 2. Stransky N, et al. *Nat Commun.* 2014;5:4846. 3. Kim J, et al. *PLoS One.* 2014;9:3. 4. Ross JS, et al. *Oncologist.* 2014;19: 235-242. 5. Vaishnavi A, et al. *Nat Med.* 2013;19:1469-1472. 6. Fernandez-Cuesta L, et al. *AACR.* 2014 (abstr 1531). 7. Brzezianńska E, et al. *Mutat Res.* 2006 Jul 25;599(1-2):26-35. 8. Wu G, et al. *Nat Genet.* 2014a;46:444-450. 9. Wiesner T, et al. *Nat Commun.* 2014;5:3116. 10. Shi E, et al. *J Transl Med.* 2016;14:339. 11. Bishop JA, et al. *Hum Pathol.* 2013;44:1982-1988. 12. Tognon C, et al. *Cancer Cell.* 2002;2:367-376. 13. Bourgeois JM, et al. *Am J Surg Pathol.* 2000;24:937-946. 14. Vaishnavi A, et al. *Cancer Discov.* 2015 Jan;5(1):25-34. 15. Rubin BP, et al. *Amer J Pathol.* 1998;153:1451-1458.

Key: AML – acute myeloid leukemia; CMN – congenital mesoblastic nephroma; CNS – central nervous system; CRC – colorectal cancer; GI – gastrointestinal; GIST – gastrointestinal stromal tumor; IFS – infantile fibrosarcoma; MASC – mammary analogue secretory carcinoma; PTC – papillary thyroid carcinoma.

Table 2. US Tumor Incidence and *NTRK* Gene Fusion Frequency

Tumor Type	US Tumor Incidence ^{a,1}	<i>NTRK</i> Gene Fusion Frequency
NSCLC	190,304 ^{b,2}	0.1%-3.3% ^{c,3,4,5}
CRC	140,250	0.5% ⁶
Melanoma	91,270	0.3% ^{d,6,7}
Thyroid carcinoma	53,990	2%-12% ^{8,9,10}
STS	13,040	0.97% ⁶
GIST	5,000 ^{e,11,12}	4.2% ^{f,13,14}
IFS	0.1% of STS ^{g,15}	90.9% ^{16,17,18}
Salivary gland	3%-6% of head and neck ^{h,19,20}	~100% (MASC only) ^{i,19,21,22,23}

References: 1. Siegel RL, et al. *Ca Cancer J Clin*. 2018;68:7-30. 2. SEER Cancer Statistics Review. Lung and bronchus. https://seer.cancer.gov/archive/csr/1975_2014/results_merged/sect_15_lung_bronchus.pdf. Accessed July 4, 2018. 3. Farago AF, et al. *Transl Lung Cancer Res*. 2017 Oct;6(5):550-559. 4. Ricciuti B, et al. *Med Oncol*. 2017;34:105. 5. Rolfo C, et al. *Lab Invest*. 2017 Nov;97(11):1268-1270. 6. Stransky N, et al. *Nat Commun*. 2014 Sep 10;5:4846. 7. Wiesner T, et al. *Nat Comm*. 2014;5:3116. 8. Sassolas G, et al. *Thyroid*. 2012 Jan;22(1):17-26. 9. Bongarzone I, et al. *Clin Cancer Res*. 1998 Jan;4(1):223-228. 10. Brzezianska E, et al. *Mutat Res*. 2006 Jul 25;599(1-2):26-35. 11. Mei L, et al. *Trends Cancer*. 2018 Jan;4(1):74-91. 12. American Cancer Society. Key statistics for gastrointestinal stromal tumors. <https://www.cancer.org/cancer/gastrointestinal-stromal-tumor/about/key-statistics.html>. Accessed May 23, 2019. 13. Brenca M, et al. *J Pathol*. 2016 Mar;238(4):543-549. 14. Shi E, et al. *J Transl Med*. 2016;14:339. 15. SEER Cancer Statistics Review. Soft Tissue Sarcomas. https://seer.cancer.gov/archive/csr/1975_2014/results_merged/sect_34_soft_tissue_sarcomas.pdf. Accessed July 4, 2018. 16. Bourgeois JM, et al. *Am J Surg Pathol*. 2000;24:937-946. 17. Pavlick D, et al. *Pediatr Blood Cancer*. 2017 Aug;64(8). 18. Davis JL, et al. *Pediatr Dev Pathol*. 2018 Jan-Feb;21(1):68-78. 19. Badlandi J, et al. *ANZ J Surg*. 2017 Oct 5. doi: 10.1111/ans.14201. 20. Barnes L, et al. IARC Press. 2005;211-215. 21. Bishop JA, et al. *Hum Pathol*. 2013;44:1982-1988. 22. Skalova A, et al. *Am J Surg Pathol*. 2018 Feb;42(2):234-246. 23. Urano M, et al. *Hum Pathol*. 2015;46(1):94-103.

^a Tumor incidence is provided from Siegel 2018 data unless otherwise specified.

^b NSCLC incidence as provided by SEER data from 2010-2014.

^c The frequency of the *NTRK* gene fusions is not well established with estimates ranging from 0.1% among all NSCLCs to 3% in patients without other oncogenic driver mutations present. *NTRK1* gene fusions account for up to 3.3% of cases of patients with adenocarcinoma. *NTRK2* and *NTRK3* gene fusions occur in ≤1% of all NSCLC types.

^d Recent data appear to show a higher rate of *NTRK* gene fusions among spitzoid melanomas compared with melanoma with 21.2% harboring a *NTRK1* gene rearrangement.

^e Per the ACS, the current estimates for new GIST cases each year in the US is 4,000-6,000.

^f This represents the percentage of patients with *NTRK* gene fusions in the GIST patient population lacking patients lacking KIT/PDGFRA/RAS pathway alterations.

^g Per SEER data from 2010-2014, the incidence of STS was 13,701.

^h Per Siegel et al 2018, the incidence of head and neck cancers for 2018 is estimated to be 51,540.

ⁱ MASC tumors of the salivary gland commonly demonstrate a characteristic gene translocation resulting in the *ETV6-NTRK3* gene fusion in nearly 100% of tumors. However, a recent analysis presented 10 cases of MASC of the salivary gland harboring *ETV6-RET* translocations. The incidence of *NTRK* gene fusions in other salivary gland histologies has not been reported to date.

Key: CRC – colorectal cancer; GIST – gastrointestinal stromal tumor; IFS – infantile fibrosarcoma; MASC – mammary analogue secretory carcinoma; NSCLC – non-small cell lung cancer; STS – soft tissue sarcoma; US – United States.

June 10, 2019

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: Open Input Period on Revisions to ICER's Value Framework for 2020

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) solicitation for input on revisions to its Value Assessment Framework for 2020. 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 continues to believe that efforts to assess a health intervention's value should be holistic and transparent. Value is a multifaceted, complex concept. As our health system strives to tie reimbursement for health care services to the value it generates, it is critical that the process and methods underlying how value is measured be agreed to by a wide array of stakeholders and reflect the most accurate and comprehensive definition of value possible.

ICER has attempted to be more responsive to concerns raised by stakeholders regarding its process for conducting value assessments. In its 2017 framework revisions, ICER made several modifications purported to better-align its process with patient-centered value assessment. We were also encouraged by the development of a separate framework to assess treatments for ultra-rare diseases – recognizing that these conditions require special consideration. However, in both process and results, these changes have not fully addressed the frameworks' lack of necessary patient-focused elements. Further, we remain concerned that the changes that were ultimately adopted have not resulted in a meaningful difference in the way these assessments are presented to and interpreted by patients, health plans, and policy makers.

As ICER contemplates revisions to its framework for future assessments, we note that many of the foundational concerns we have raised in past comments remain unaddressed. These deficiencies significantly limit the framework's ability to accurately convey the full value of a

therapy. As a starting point for the 2020 revisions, ICER should prioritize modifications to ensure that its framework no longer:

- Inappropriately conflates the impact of a therapy on patient health outcomes, including quality of life, with the potential budget impact to any individual payer or group of payers;
- Fails to uniformly rely on robust and validated methodological standards, and apply those standards consistently and transparently; and
- Falls short of fulfilling ICER's stated goal of "fairly reward[ing] innovators for the value they bring to patients, and provide them ample incentive to pursue the investments and research that will lead to the innovative treatments of tomorrow."

Correcting these issues should be of paramount importance to ICER as it works to improve its framework for 2020.

In addition to the overarching modifications above, we believe there are several additional elements ICER could include in its assessment process that would provide greater transparency, capture more elements of value, and better contextualize assessments given the specifics of the disease under examination.

- **Substantive incorporation of real-world evidence (RWE) and contextual considerations into assessment metrics.** We appreciate ICER's acknowledgement that the science of value assessment is moving beyond traditional cost-effectiveness measures, and should now include additional elements that, collectively, present a more holistic picture of an intervention's value to both the patient and the health care system. But while RWE and new report sections on contextual considerations and other benefits are summarized qualitatively in ICER's work, these measurements are not incorporated quantitatively into ICER's suggested value-based price metric. We recommend ICER take this opportunity to explore innovative methods to meaningfully incorporate both RWE and contextual considerations into its assessments. Ultimately, ICER should consider the full spectrum of available evidence. This is particularly important in the context of assessments of therapies for rare diseases, where randomized controlled trials often fail at capturing clinical heterogeneity.

One obvious impediment to the incorporation of RWE into its reports is ICER's decision to evaluate products that have not yet, or only just recently, been brought to market. ICER should allow sufficient time to elapse after a product is approved and marketed so that RWE can be developed and incorporated.

Similarly, we believe the absence of a material impact of a therapy's "contextual considerations" on ICER's value-based price metric significantly limits the report's applicability to real world pricing and coverage decisions. Such contextual

considerations include not only savings or cost-offsets associated with a given therapy when compared with the current standard of care, but also with patient preferences regarding site of care, method of administration, reduction in important health disparities, broader family burden, etc.

We encourage ICER to work collaboratively with stakeholders on appropriate methods that will substantively incorporate these dimensions of value into its analyses. We also recommend ICER develop a formal mechanism to capture the patient's perspective when considering a therapy's value and qualify it in a meaningful way.

- **Adapting assessments to the specifics of the disease area.** ICER should modify its methodology to include metrics specific to the disease state that the intervention addresses. While we recognize the need for common cost-effectiveness methods across conditions, ICER should include disease-specific measures that will be important for stakeholders to consider. This is of acute concern in the context of treatments for rare or orphan diseases in which treatment benefit may be hard to capture with ICER's conventional methods. In addition, there are many serious conditions where elements such as the quality of life for a caregiver, the impact on the family unit, and unmet need are important components of measuring a therapy's value. Currently, we feel that ICER does not appropriately consider these impacts in its assessments.
- **Further address the deficiencies of the quality adjusted life year (QALY).** We continue to object to use of the QALY as the fundamental metric of ICER's review. While we appreciate ICER's recognition of the QALY's shortcomings in developing the equal value of life year gained (evLGY) metric, we believe more must be done to communicate concerns around QALYs and how their use can impede the goals of personalized medicine.
- **Acknowledgment when assessment results are missing key elements or are unreliable.** We remain concerned that ICER's reports do not appropriately convey when – because of methodological or other reasons – their results may not be applicable to real-world pricing and coverage decisions. The science and methods of value measurement are constantly being deliberated and refined. Yet often ICER's reports present results as if the science of value measurement were static. For example, although ICER stresses the importance of taking the long-term perspective on a treatment's benefits and costs, current limitations in methods sometimes prevent adequate modeling of this perspective at the time of ICER's assessment. The lack of cost-effectiveness methods that account for the long-term perspective in certain disease states necessarily limits the value of ICER's results to readers – and particularly those health care professions who may make clinical or benefit decisions based on ICER's results.

We urge ICER to be more upfront about this discussion and acknowledge when assessment results are lacking key data points that could inform decision-making or when there is not agreement about a particular measurement. One solution could be to include confidence intervals around key measurements that reflect uncertainty. ICER should also provide guidance to the public as well as payors about how the results of its analysis should and should not be interpreted. Finally, every ICER report should include a clear statement of the assessment's limitations in order to minimize misinterpretation or inappropriate use.

- **Changes to ICER's framework for ultra-rare diseases.** We continue to believe that ultra-rare and orphan diseases present unique challenges for traditional value assessment techniques that have not been addressed by this separate framework. The criteria ICER chose to determine when this separate framework will be used are arbitrary and overly rigid, and fail to capture the profound complexity and nuance of rare diseases. Since no statutory authority or regulatory body in this country has developed a definition of "ultra-rare," we recommend ICER 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 or fewer 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. We also urge ICER to account for smaller patient populations, trial size, and other factors that differentiate orphans from other drugs in its assessment of these medicines.

We hope ICER will adopt these recommendations as it begins the process of modifying its Value Framework for 2020. BIO will be providing detailed comment on proposed revisions later this year. If you have any questions regarding our comments or if we can be of further assistance, please do not hesitate to contact us at (202) 962-9200.

Sincerely,

/s/

Crystal Kuntz
Vice President
Healthcare Policy and Research

June 10, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Public Input for 2020 Value Assessment Framework

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson,

Boehringer Ingelheim (BI) appreciates the opportunity to provide feedback on the revisions to ICER's 2020 Value Assessment Framework. BI believes that collaboration, transparency, and open dialogue throughout the development of ICER's value assessment framework is critical to ensuring appropriate and accurate evaluations of treatments according to what patients and stakeholders value. BI supports ICER's efforts to base health policy decisions on the best available evidence and commends ICER for seeking public input into its proposed revisions to the Value Assessment Framework. Our comments aim at strengthening ICER's methods and operational approach to assessing value.

Cost Effectiveness Models

ICER has sought to address limitations with its initial approach to modeling cost effectiveness, including the introduction of Equal Value Life Years Gained (EvLYG); however, the changes do not address several limitations of the original approach. EvLYG is not adequate for capturing and articulating the value of several types of innovative products.

- (1) In some therapeutic areas, like oncology, new products are introduced as options for patients who have tried and failed other available treatments and depending on the effectiveness of the product in later lines of therapy, it may be developed for use earlier in treatment, either earlier in the treatment pathway or for less advanced cancers. Neither cost/QALY nor EvLYG based on the initial indications of a new product capture its full value at the end of its development program. Valuing a product using EvLYG and cost/QALY based on the initial indication may result in halting its development for earlier stage tumors and earlier steps in the treatment pathway, thereby not allowing

patients to benefit fully from the innovation. Any value assessment should consider how a product can evolve with additional clinical evidence and data to support new indications and uses in the future.

BI recommends when evaluating a product in late or end stage conditions or in later lines of therapy (e.g., in oncology, rheumatoid arthritis, etc.) that ICER note that the cost effectiveness ratio will change in earlier stages of disease or earlier lines of therapy and warrants reassessment in the future.

- (2) Neither cost/QALY nor EvLYG can capture fully the value of innovative treatments for conditions that have a large effect on physical function and patient well-being, are not life threatening or life limiting, such as rheumatoid arthritis, rare forms of psoriasis, and other inflammatory chronic conditions. The Federal Drug Administration (FDA) recently launched an initiative to develop a guidance for patient-focused drug development¹, emphasizing the importance of the patient perspective for product development. Benefits to patients play an important role in the value of a particular drug and therefore need to be considered in any value assessment.

BI recommends that ICER incorporate contextual details of value that are not captured by EQ5D and other utility measures into their assessments.

- (3) Currently ICER does not include indirect costs in its cost effectiveness analyses and provides those analyses separately. Limiting the cost effectiveness analyses to direct health care costs is misleading when assessing the value of a product from the societal/patient perspective and from the point of view of self-insured employers.² By broadening the scope of value assessments, ICER will strengthen the output of these assessments and make them more meaningful for a wider range of stakeholders, especially when evaluating chronic conditions characterized by significant functional limitations.

BI recommends including indirect costs related to productivity, caregiver burden, disability, and symptom management in the cost effectiveness models.

Selection of Patient Populations

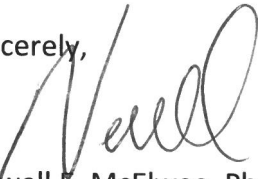
Selection of the patient population for a value assessment is a first step in ensuring relevance. ICER has created a category of diseases called, ‘serious ultra rare’, defined as having fewer than 10,000 patients in the US. It is not clear how this definition will be applied to different patient subgroups, as the definition is specific to ICER and not shared by other organizations or regulatory agencies. While some therapeutic areas such as oncology are relying increasingly on biomarkers and genotypic classifications of tumors and patients, other therapeutic areas use phenotypic classifications based on signs and symptoms, (e.g., small bowel Crohn’s disease,

primary progressive multiple sclerosis, plantar palmer psoriasis, lupus nephritis, etc.). Allowing for both genotypic and phenotypic classifications of conditions and patients is important for reflecting emerging scientific and clinical paradigms for targeted treatment.

BI recommends the use of accepted (e.g., by regulatory authorities) definitions³ of orphan and rare diseases and using phenotypic and biomarker-based classifications of patient groups. We stress the importance of considering each distinct patient population separately when evaluating a single product with multiple indications within a therapeutic area, and when evaluating a therapeutic class in which products are indicated for distinct patient populations (e.g., adult and pediatric).

BI supports ICER's efforts toward greater transparency and the use of real world evidence in its value assessments, and looks forward to closer collaboration between ICER, drug manufacturers, and other stakeholders such as practicing clinicians and patients. The incorporation of these recommended changes and increasing transparency can aid in increased relevance and broader acceptance of ICER's future value assessments.

Sincerely,



Newell E. McElwee, PharmD, MSPH
Vice President, US Health Economics Outcomes Research
Boehringer Ingelheim Pharmaceuticals, Inc.

References

¹ “Patient-Focused Drug Development Guidance: Methods to Identify What is Important to Patients and Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments.” <https://www.fda.gov/drugs/news-events-human-drugs/patient-focused-drug-development-guidance-methods-identify-what-important-patients-and-select>. Accessed June 10, 2019.

² Paulden, M. “PRM13 - The Flawed Recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine.” Value in Health, Volume 21, S357 - S358.

³ “Developing Products for Rare Diseases & Conditions.” <https://www.fda.gov/industry/developing-products-rare-diseases-conditions>. Access June 10, 2019.



Bristol-Myers Squibb

U.S. Pharmaceuticals
P. O. Box 4500, Princeton, NJ 08543-4500

June 10, 2019

Steven D. Pearson, M.D., M.Sc. FRCP President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109

RE: Call for Public Input on ICER's Value Assessment Framework

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson,

Bristol-Myers Squibb Company (BMS) is pleased to respond to the Institute for Clinical and Economic Review's (ICER) call for suggestions on how to improve its value assessment framework. BMS also supports the industry trade association comments submitted by BIO, NPC and PhRMA.

As a research and development (R&D)-focused organization, we believe in the power of science to address some of the most challenging diseases of our time. We have a high bar for innovation focused on areas where our medicines can truly make a difference for patients. Our focus on these unmet needs comes at an unprecedented time, where scientific breakthroughs are advancing the treatment of disease like never before.

Fueled by robust R&D capabilities, we are advancing science through internally discovered medicines as well as new discoveries we bring into the company through academic, biotech and biopharma partnerships. This is true in each of our four therapeutic areas: Oncology, Immunoscience, Cardiovascular and Fibrosis.

Our scientists are passionate in their pursuit of new and better medicines, knowing that there are patients who currently have few or no options. We have a legacy of transforming patient outcomes in major diseases such as cancer, cardiovascular disease, HIV and HCV. We pioneered a class of medicines that harness the power of the immune system to treat cancer. Our decades of work in cancer have resulted in major advances in life extending therapies and improved survival; progress that the majority of Americans value highly.¹ We are also pursuing medicines with transformational potential in diseases such as heart failure, liver fibrosis and rheumatoid arthritis.

With incredible advances in technology and diagnostic capabilities, we are leveraging translational medicine and data analytics to understand how we can deliver the right medicine to the right patient at the right time to achieve the best outcome. BMS is also dedicated to sharing and disseminating the results of our research to ensure that our research can benefit the widest range of patients; we share our clinical trial data through scientific congress and peer-reviewed journals.

BMS acknowledges the importance of promoting a rigorous, comprehensive and inclusive

¹ Harvard T.H. Chan School of Public Health. (2016, March). *American Attitudes About Cancer*. Retrieved March 20, 2017, from <https://cdn1.sph.harvard.edu/wp-content/uploads/sites/94/2016/03/Stat-Harvard-Poll-Mar-2016-Cancer.pdf>



Bristol-Myers Squibb

U.S. Pharmaceuticals

P. O. Box 4500, Princeton, NJ 08543-4500

approach to value that aligns with best practices in value assessment. The comments and recommendations that follow below are shared with this approach in mind.

ICER overemphasizes value assessment of prescription drugs, while largely ignoring non-drug interventions.

Recent data show that prescription drug spending makes up only approximately 14% of national health expenditures in the US,² yet the large majority of ICER's efforts are focused solely on prescription drug interventions. In doing so, ICER is missing out on an opportunity to have a credible and meaningful impact on the value debate in the US. The rising cost of healthcare in the US will never be adequately addressed by focusing solely on prescription drug costs, which make up a small minority of overall healthcare expenditures. In particular, consider the evidence that increases in drug spending can actually reduce overall healthcare costs and improve quality, as so aptly demonstrated by Lee Newcomer in his 2014 Journal of Oncology Practice study.³ ICER's overemphasis on prescription drugs certainly does not come without repercussions to patients and society. The overemphasis that ICER places on prescription drug costs attempts to emulate health technology assessments (HTA) used in ex-US settings, which have come at the expense of access to treatment. Numerous studies have shown that access to, and uptake of, new cancer medicines lag in countries with HTAs that place a heavy focus on drug costs compared to the US.^{4,5,6,7,8} Such limited access has significant impact on patients and society, for example lower survival rates for oncology patients in these countries.⁹

We believe that ICER's overemphasis on drug costs and inclusion of budget impact may result in several consequences, including but not limited to:¹⁰

1. Care rationing, as observed in ex-US settings^{11,12,13,14,15}

² Roehrig C. Center for Sustainable Health Spending Data Brief: A Ten Year Projection of the Prescription Drug Share of National Health Expenditures Including Non- Retail. Altarum Institute. May 2017. <https://altarum.org/sites/default/files/uploaded-publication-files/Non-Retail%20Rx%20Forecast%20Data%20Brief%20with%20Addendum%20May%202017.pdf>. Accessed June 7, 2019.

³ Newcomer LN. Innovative payment models and measurement for cancer therapy. J Oncol Pract. 2014; 10:187–189.

⁴ Mason, A., Drummond, M., Ramsey, S., Campbell, J., & Raisch, D. (2010). Comparison of anticancer drug coverage decisions in the United States and United Kingdom: does the evidence support the rhetoric?. Journal of Clinical Oncology, 28(20), 3234-3238.

⁵ Jönsson, B., Hofmarcher, T., Lindgren, P. E. T. E. R., & Wilking, N. I. L. S. (2016). Comparator report on patient access to cancer medicines in Europe revisited. IHE report, 4.

⁶ Quintiles. (2016, July). HTA Uncovered. 12. Retrieved March 20, 2017, from <http://www.quintiles.com/library/white-papers/hta-uncovered-july-2016>

⁷ Bergmann, L., Enzmann, H., Broich, K., Hebborn, A., Marsoni, S., Goh, L., ... & Zwierzina, H. (2013). Actual developments in European regulatory and health technology assessment of new cancer drugs: what does this mean for oncology in Europe?.

⁸ Rawson, N. (2014, June). Has pCODR Improved Access to Oncology Drugs? Retrieved from Fraser Institute:

<https://www.fraserinstitute.org/sites/default/files/has-pCODR-improved-access-to-oncology-drugs-rev.pdf>

⁹ Allemani, C., Weir, H. K., Carreira, H., Harewood, R., Spika, D., Wang, X. S., ... & Marcos-Gragera, R. (2015). Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). The Lancet, 385(9972), 977-1010.

¹⁰ Lakdawalla, D., & Neumann, P. J. (2016, September 22). Budget Criteria And Drug Value Assessments: A Case Of Apples And Oranges? Retrieved from Health Affairs Blog: <http://healthaffairs.org/blog/2016/09/22/budget-criteria-and-drug-value-assessments-a-case-of-apples-and-oranges/>

¹¹ National Health Service. (2017, March 2). National Cancer Drugs Fund List. Retrieved March 20, 2017, from <https://www.england.nhs.uk/wp-content/uploads/2017/03/national-cdf-list-v1-21.pdf>

¹² NICE. (2017, January 11). Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib. doi:978-1-4731-2263-5.

¹³ National Health Service. (2016, May). Standard Operating Procedures: The Cancer Drug Fund (CDF). Retrieved March 20, 2017, from

<https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf>

¹⁴ National Institute for Health and Care Excellence. (2016, March 16). Faster access to effective cancer treatments through the new Cancer Drugs Fund. NICE. Retrieved March 22, 2017, from <https://www.nice.org.uk/news/article/faster-access-to-effective-cancer-treatments-through-new-cancer-drugs-fund>

¹⁵ National Institute for Health and Care Excellence (NICE). (2014). Evidence Summary: new medicine (ESNM32). Relapsed and refractory multiple



Bristol-Myers Squibb

U.S. Pharmaceuticals

P. O. Box 4500, Princeton, NJ 08543-4500

2. Influencing coverage decisions that will lead to reduced patient access^{16,17}
3. Disincentivizing the development of innovative and groundbreaking therapies, such as those in immuno-oncology which have been shown to result in long-term value^{18,19,20}

ICER should be cognizant and transparent up front about these and any other potential unintended consequences of their work, and we strongly recommend that ICER carefully re-examine their agenda of focusing their efforts on prescription drugs.

ICER continues to rely on the traditional QALY and arbitrary cost-per-QALY thresholds, at the risk of perpetuating flawed conclusions and judgements on value.

ICER retains its problematic reliance on the quality-adjusted life year (QALY), which is universally acknowledged to have limited utility in real-world discussions.^{21,22,23} The QALY is a reductionist measure that has been shown to be insufficient in meaningfully measuring the quality of life of patients.²⁴ Importantly, QALYs are particularly poor at assessing true value among the elderly, patients with disabilities as well as those with chronic diseases, and are a departure from the movement towards more patient-centered measures.²⁵

A cost-effectiveness threshold based on QALYs is also ill suited for application in the US setting and around the world. In fact, ICER cites examples from low- and middle-income countries as well as Latin America when proposing a cost-effectiveness threshold,²⁶ which have very different healthcare settings than the US. The US healthcare system is a complex, heterogeneous system comprised of multiple decision-makers. A single, national cost effectiveness (CE) threshold does not make sense in a setting where decision-making is dispersed across both public and private stakeholders, as well as at the national, regional, and local level. ICER should look towards a solution that is applicable in the US setting, that reflects the complexity of the US healthcare system, rather than apply methods derived from single payer systems and uniform viewpoints of value.

Further, ICER retains its use of arbitrary cost effectiveness thresholds. As one of the members on International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) expert panel

myeloma: pomalidomide.

¹⁶ Perfetto, E.M., Oehrlein, E.M., Boutin, M., Reid, S. (2017). Value to Whom? The Patient Voice in the Value Discussion. *Value in Health*, 20, 286-291.

¹⁷ Xcenda. Applying Cost-Effectiveness Thresholds to the Real World: Implications on Access for Medicare Beneficiaries. Available at: https://www.xcenda.com/-/media/assets/xcenda/english/content-assets/white-papers-issue-briefs-studies-pdf/xcenda-pharma_icer_issue_brief_may2018.pdf?la=en&hash=2F6CBF56A6C7576C997C20E52A107D4E20506678

¹⁸ Johnson, P., Greiner, W., Al-Dakkak, I., & Wagner, S. (2015). Which metrics are appropriate to describe the value of new cancer therapies?. *BioMed research international*, 2015.

¹⁹ Othus, M., Bansal, A., Koepl, L., Wagner, S., & Ramsey, S. (2016). Accounting for Cured Patients in Cost-Effectiveness Analysis. *Value in Health*.

²⁰ Ciarametaro, M., Abedi, S., Sohn, A., Ge, C. F., Odedara, N., & Dubois, R. (2017). Concerns around budget impact thresholds: not all drugs are the same. *Value in Health*, 20(2), 230-233.

²¹ Pettitt, D., Raza, S., Naughton, B., Roscoe, A., Ramakrishnan, A., Ali, A., . . . Brindley, D. (2016). The Limitations of QALY: A Literature Review. *Journal of Stem Cell Research & Therapy*.

²² Kind, P., Lafata, J. E., Matuszewski, K., & Raisch, D. (2009). The use of QALYs in clinical and patient decision-making: issues and prospects. *Value in Health*, 12, S27-S30.

²³ Sawhney TG, Pyenson B, Buzby E. "The utility of ICER reports for private payer drug coverage decision-making: Cost-effectiveness assessments." September 19, 2018. Available at: <http://www.milliman.com/insight/2018/The-utility-of-ICER-reports-for-private-payer-drug-coverage-decision-making-Cost-effectiveness-assessments/>

²⁴ Knapp, M, Mangalore, R. "The trouble with QALYs ...". *Epidemiol Psychiatr Soc* 2007; 16: 289-93.

²⁵ Pettitt D, Raza S, Naughton B, Roscoe A, Ramakrishnan A, Ali A, Davies B, Dopson S, Hollander G, Smith J et al (2016) The limitations of QALY: a literature review. *Journal of Stem Cell Research & Therapy* 6(4). <https://doi.org/10.4172/2157-7633.1000334>

²⁶ Institute for Clinical and Economic Review. (2017, February 1). *Overview of the ICER value framework and proposals for an update for 2017-2018*. <http://icer-review.org/wp-content/uploads/2016/02/ICER-VAF-Update-Proposals-020117.pdf>



Bristol-Myers Squibb

U.S. Pharmaceuticals

P. O. Box 4500, Princeton, NJ 08543-4500

examining the use of QALYs for CEA noted, “\$50,000 per QALY [is] an arbitrary but conveniently round number, [which then] settled into conventional wisdom.”²⁷ ICER should not use an explicit threshold to judge cost effectiveness, and in turn, value.

ICER’s use of a short, five-year time frame to assess “affordability” is also problematic. Numerous studies have shown that the value of therapies evolves over time, and particularly for conditions such as cancer, long-term survival beyond five years is of particular importance.²⁸ Additionally, traditional clinical trials generally report median overall survival (OS), as well as progression-free survival as trial endpoints. These commonly used endpoints may considerably undervalue the impact of newer cancer therapies that have the potential to provide long-term survival or even cures.²⁹ A recent study examining the cost-effectiveness of immunotherapy for patients with advanced melanoma found an incremental cost-effectiveness ratio of \$324,000/QALY using traditional endpoints, but a much lower incremental cost effectiveness ratio of \$113,000/QALY when cure fractions were incorporated into the model.³⁰ Particularly for newer, emerging oncolytics, ignoring the long-term survival and metrics such as cure fractions may result in a significantly erroneous assessment of value.

Finally, the framework, including the proposed CEA, has the potential to broadly disadvantage patient access to innovative products. For example, a recent study showed that if Medicare Part B were to apply the cost-effectiveness thresholds utilized by ICER as the basis for coverage policy, 62% to 93% of patients with serious, complex conditions would face access barriers to clinically important physician-administered treatments.³¹ For patients and providers this would mean a significant loss of choice. Value cannot be determined solely by cost, but instead we must keep the patient at the center of whatever assessment of value that we do. There is a big disconnect between how patients define value and how health economists define value. ICER should ensure that the patient/family view and impact on the patient’s quality of life are at the forefront of any attempt to assess value. If value assessments captured the true social value of treatments – such as improvements in patient productivity and reductions in caregiver burden – it’s likely that the results that come out of the assessment would fall significantly under the arbitrary cost/QALY thresholds set by entities such as ICER. The scientific community’s understanding of the full range of benefits of breakthrough products – an important input in assessing cost effectiveness – evolves over time, and ICER’s methodology does not take this into account. In a rush to assess new treatments, ICER is often unable to include real-world, non-trial data collected from post-market studies, patient registries, and electronic health records (EHR), which can substantially change our understanding of the value of innovative medicines. These data are often only available long after product launch, and provisions should be made to include these data, or at minimum, ICER should explicitly note that assessments of new technologies are incomplete and provisional in nature. As noted by ISPOR’s Task Force on Good Research Practices for CEA, “the time horizon for trials often does not reflect the duration of impact of the intervention” and that “cost effectiveness observed within [a] trial may be substantially different

²⁷ Neumann, P. J., Cohen, J. T., & Weinstein, M. C. (2014). Updating cost-effectiveness—the curious resilience of the \$50,000-per-QALY threshold. *New England Journal of Medicine*, 371(9), 796-797.

²⁸ Allen, J. D., Stewart, M. D., Roberts, S. A., & Sigal, E. V. (2017). The value of addressing patient preferences. *Value in Health*, 20(2), 283-285.

²⁹ Johnson, P., Greiner, W., Al-Dakkak, I., & Wagner, S. (2015). Which metrics are appropriate to describe the value of new cancer therapies?. *BioMed research international*, 2015.

³⁰ Othus, M., Bansal, A., Koepf, L., Wagner, S., & Ramsey, S. (2016). Accounting for Cured Patients in Cost-Effectiveness Analysis. *Value in Health*.

³¹ Xcenda. Applying Cost-Effectiveness Thresholds to the Real World: Implications on Access for Medicare Beneficiaries. Available at: https://www.xcenda.com/-/media/assets/xcenda/english/content-assets/white-papers-issue-briefs-studies-pdf/xcenda-pharma_icer_issue_brief_may2018.pdf?la=en&hash=2F6CBF56A6C7576C997C20E52A107D4E20506678



Bristol-Myers Squibb

U.S. Pharmaceuticals

P. O. Box 4500, Princeton, NJ 08543-4500

from what would have been observed with continued follow-up.”³²

ICER’s approach to value assessment is static, and thus the information generated from its value assessment framework is often quickly outdated and lacks relevance and applicability.

ICER does not provide a clear timeline or criteria for updating their value assessments and often wrongly assumes that patient values are uniform and unchanging across patient populations. Not only is the scientific field dynamic, but patient beliefs with regard to treatment-related value varies as a result of differences in population level and individual determinants. In order to achieve a more dynamic approach, we encourage ICER to meaningfully integrate the patient perspective and to consider the practical steps several patient advocacy groups have outlined for the update to the value assessment framework.³³

Particularly for the field of oncology, where the understanding of a new therapy may evolve over time, it is important for ICER to provide a clear caveat or “expiration date” for their value assessments and a greater acknowledgment about the degree of uncertainty of their models. For example, in the field of immuno-oncology, more advanced methods have been developed since these treatments received regulatory approval. Through longer term follow-up data from randomized clinical trials (RCTs), researchers have validated that more flexible models for these treatments can better capture the complex hazard functions observed in RCTs.³⁴ In rapidly changing therapeutic areas like oncology, it is important that ICER acknowledge the degree of uncertainty in its modeling and recognize that more advanced modeling techniques may later be found to be more appropriate.

While ICER has conducted a few “condition updates”, there needs to be more a more clear and formal mechanism for stakeholders to request corrections and relevant updates when new evidence becomes available, particularly long-term data and real-world evidence. This is particularly true for newer, breakthrough therapies, as the evidence base and science may be moving quickly, and ICER’s static value assessments risk perpetuating outdated science and the potential for ill-informed decisions to be made based on ICER’s work. For example, ICER released their evidence report of non-small cell lung cancer (NSCLC) related therapies on September 29, 2016, and before the committee was even able to meet, the evidence report was out of date due to the approval of Tecentriq® on October 18, 2016.^{35,36} Knowing this, ICER should hold itself accountable to its work and periodically validate the accuracy of its value assessments as new data and science emerges, which can be achieved by regularly retrospectively re-assessing the accuracy and relevance of their value assessments against new and/or real-world data.

³² Ramsey, S., Willke, R., Briggs, A., Brown, R., Buxton, M., Chawla, A. et al. (2005). Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value in health*, 8(5), 521-533.

³³ Addario BJ, Fadich A, Fox J, Krebs L, Maskens D, Oliver K, et al. Patient value: Perspectives from the advocacy community. *Health Expect*. 2018;21(1):57–63.

³⁴ Bullement A, Latimer NR, Gorrod HB. Survival Extrapolation in Cancer Immunotherapy: A Validation-Based Case Study. *Value in Health*. 2019:276-283.

³⁵ Institute for Clinical and Economic Review. (2016, November 1). *Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness, Value and Value-Based Price Benchmarks*. https://icer-review.org/wp-content/uploads/2016/10/MWCEPAC_NSCLC_Final_Evidence_Report_Meeting_Summary_110116.pdf

³⁶ U.S. Food and Drug Administration. (2016, October 18). *BLA 761041 Approval Letter*. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/761041Orig1s000ltr.pdf



Bristol-Myers Squibb

U.S. Pharmaceuticals

P. O. Box 4500, Princeton, NJ 08543-4500

Separate Any Budget Impact Analysis from Value Assessments

While it is important to acknowledge that healthcare consumption and treatment have an impact on expenditures, we continue to believe that ICER should completely separate estimating short-term affordability from their value assessment framework. Budget impact analyses have nothing to do with value, and are based on arbitrary caps on innovation that do not allow for trade-offs between cost centers. While we appreciate that ICER has taken steps to improve the short-term affordability component of its framework, short-term budget impact is a measure of resource use and should remain separate from value or affordability assessment. ICER's narrow focus ignores the total costs of care and overlooks the multifaceted, complex process of providing care to patients in which interventions are rarely provided in isolated silos. If ICER is truly interested in budget impact it should modify its current agenda of focusing nearly solely on prescription drugs, which make up a small minority of health expenditures in the US, and dedicate its resources to other parts of the healthcare sector where much bigger financial impacts and potential savings could be achieved.

ICER also holds the share of budget dedicated to medications constant, overlooking the fact that treatment protocols evolve over time. For example, in 1987, cancer treatment accounted for 4.81 percent of total expenditures across all payers, with 64 percent of all cancer-related spending dedicated to inpatient procedures. In contrast, prescription medicines and outpatient costs accounted for less than 33 percent of total cancer spend in 1987. By 2005, cancer treatment still comprised less than 5 percent of total healthcare spending in the U.S. (4.91 percent); however, inpatient hospitalizations had fallen to 27.5 percent of total costs as treatment shifted to outpatient procedures and medications (63.1 percent).³⁷ Thus, ICER's static apportionment of healthcare spending amongst the various types of interventions ignores the fact that the healthcare system is dynamic and treatment patterns and protocols change over time.

While ICER acknowledges the difficulty in providing a general, population-level utilization and uptake scenario, and assessments include a range of plausible uptake estimates, the final 2017-19 framework retained an "affordability and access alert" that would rely on selecting a single uptake scenario despite ICER's acknowledgement of the difficulty in estimating what "will actually happen in the marketplace."³⁸ This difficulty in assessing market uptake was demonstrated in ICER's assumptions for its evaluation of PCSK9 inhibitors. In nine months, there were only 9,500 prescriptions written for the first PCSK9 to hit the market, while ICER's budget impact model estimated more than half a million prescriptions within the first year.³⁹ The difficulty in forecasting budget impact of new therapies was also demonstrated in a recent study examining ICER reports. The analysis found that ICER's uptake estimates exceeded real-world estimates by factors ranging from 7.4 to 54.⁴⁰ While ICER has improved estimates by incorporating SSR Health data on aggregate discounts and rebates, we believe the systematic bias found in budget impact estimates

³⁷ Tangka, F. K., Trogon, J. G., Richardson, L. C., Howard, D., Sabatino, S. A., & Finkelstein, E. A. (2010). Cancer treatment cost in the United States. *Cancer*, 116(14), 3477-3484.

³⁸ Institute for Clinical and Economic Review. (2017, February 1). *Final Value Assessment Framework: Updates for 2017-19*. Retrieved June 3, 2019, from <https://icer-review.org/material/final-vaf-2017-2019/>

³⁹ Tice, J. A., Ollendorf, D. A., Cunningham, C., Pearson, S. D., Kazi, D. S., & Coxson, P. G. (2015). PCSK9 inhibitors for treatment of high cholesterol: effectiveness, value, and value-based price benchmarks: final report.

⁴⁰ Snider JT, Sussell J, Tebeka MG, Gonzalez A, Cohen JT, Neumann P. (2019). Challenges with Forecasting Budget Impact: A Case Study of Six ICER Reports. *Value in Health* 22:332-339.



Bristol-Myers Squibb

U.S. Pharmaceuticals

P. O. Box 4500, Princeton, NJ 08543-4500

calls into question not only the accuracy of ICER's estimates, but the entire utility in including these estimates at all. The demonstrated lack of accuracy in published budget estimates only obfuscates an already complex discussion by introducing upwardly biased estimates into a discussion that should focus solely on clinical effectiveness. ICER appears to acknowledge its past difficulties in estimating patient uptake for new drugs. However, the decision to shift the responsibility for the prediction of patient uptake to the Policy Roundtable participants does not resolve the past issues since they are in no better position to perform such an analysis. Instead, ICER should rely on guidance from stakeholders to assess utilization estimates.

Importantly, another unintended consequence of artificial affordability thresholds is the disincentives this creates for the development of drugs for broad populations with unmet need. Predicted budget impact would increase as the number of patients increases, more likely triggering an "affordability alert" threshold. ICER arbitrarily establishes budget caps for societal expenditures on medical innovations and fundamentally ignores the value of innovation in healthcare. This approach assumes patients subjected to a cancer of high incidence or prevalence are worth 'less' than patients who have a more rare form of cancer, creating disincentives for innovation and healthcare investment. Further, by setting budget criteria ICER deters innovators from developing therapies that could benefit a broader patient population. Nevertheless, treatments that provide significant benefits to a large number of patients are exactly the treatments most desired by society. It is fundamentally flawed to assume patients subjected to a cancer of high incidence or prevalence are worth "less" than patients who have a rarer form of cancer. Conversely, a comprehensive assessment that considers societal values and broader public health issues would likely generate higher spending allocation for such therapies.

Summary & Conclusion

BMS supports defining value from the patient perspective, with an emphasis on patient-centric outcomes, desires, goals, and experiences. Moreover, healthcare is a complex, multifaceted process, and thus individual treatments and therapies should not be considered in isolation. BMS believes value assessment should be a rigorous, comprehensive approach that sufficiently addresses patient and disease heterogeneity, and the plethora of different treatments, interventions, and diagnostic tests that patients receive along the entire continuum of care. If the goal of ICER is to truly contribute high-quality information to the healthcare value dialogue, then ICER's current value assessment approach of developing prescription drug-focused, static, one-off evidence reports that evaluate a single treatment in isolation utilizing traditional cost-effectiveness analysis is wholly insufficient. Along with principles developed by the Healthcare Leadership Council,⁴¹ we support the development of value frameworks that meet these eight criteria:

- Measure value, focusing on long-term improvements in health care and societal benefit;
- Are adequately tested, transparent, reproducible, and open to formal peer review and are regularly updated to keep pace with medical advancements;
- Are based on health economics methodologies that are consistent with acceptable standards;
- Are dynamic: accommodate individual patient preferences and are regularly updated to keep pace with medical advancements;

⁴¹ Healthcare Leadership Council. Principles on Value Assessment Frameworks. 2017. Available at <https://www.hlc.org/app/uploads/2017/05/HLC-Final-Principles-on-Value-Frameworks.pdf>



Bristol-Myers Squibb

U.S. Pharmaceuticals

P. O. Box 4500, Princeton, NJ 08543-4500

-
- Focus broadly on all aspects of the health care system, not just medications;
 - Avoid biopharmaceutical budget caps that unduly delay patient access to innovation;
 - Include sensitivity analyses that are addressed when material; and
 - Incorporate clinical benefits and harms in a manner that recognizes the heterogeneity of the treatment effect as well as the average response

BMS is taking this opportunity to comment and suggest improvements to ICER's value assessment framework because of the importance that our company places on maintaining an innovation ecosystem to discover, develop and deliver transformational treatments for patients in the US and globally. BMS has outlined a number of areas in ICER's framework that, if improved, could strengthen ICER's methodology and approach. We hope that ICER incorporates these recommendations into their processes.

Sincerely,

Mitch K. Higashi, PhD

Head of US Medical Health Economics and
Outcomes Research



ECONOMIC RESEARCH CENTER at THE BUCKEYE INSTITUTE

June 10, 2019

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

RE: ICER's Call for Public Input for 2020 Value Assessment Framework

Dear Dr. Pearson:

We appreciate ICER's willingness to receive comments on its Value Assessment Framework. As researchers involved in policy discussions, we understand the importance of constructive feedback for improving methods, research, and analysis; and we hope that our comments will help enhance ICER's own methodology.

QALYs and Alternative Metrics

ICER's valuation framework aims to improve efficiency in the healthcare system by reducing waste, reducing costs, and increasing effectiveness.¹ Unfortunately, a significant literature shows that ICER's method of using the cost per quality-adjusted life year (QALY) metric in its incremental cost-effectiveness analysis to evaluate medical interventions, devices, and drugs will not, in fact, yield the improvements or savings that ICER claims.

There are several methods for assessing the value of medical interventions, each with their own set of assumptions and perspectives. The broad goal is to base decisions on comparisons across difficult-to-compare criteria that require careful, rigorous methods. Comparing ICER's framework to other methodologies reveals the benefits and shortcomings of ICER's cost-utility analysis, a subset of cost-effectiveness analysis that tries to measure and account for subjective personal benefit (such as personal preferences and qualitative wellness) in its value determinations. Other relevant frameworks include, for example, extended cost-effectiveness analysis (ECEA) and multicriteria decision analysis (MCDA).

ECEA considers value across three areas: health gains; financial risk protection; and social cost. By gathering information across numerous affected subpopulations, ECEA can measure asymmetrical effects and inequities, but does not provide a single, comparable, nonmonetary metric.² Although ECEA does not offer a single metric for comparing very different interventions,

¹ Institute for Clinical and Economic Review, "**Overview of the ICER value assessment framework and update for 2017-2019**," May 8, 2018.

² Charles E. Phelps, Darius N. Lakdawalla, Anirban Basu, Michael F. Drummond, Adrian Towse, and Patricia M. Danzon, "**Approaches to Aggregation and Decision Making—A Health Economics Approach: An ISPOR Special Task Force Report**," *Value in Health*, Volume 21, Issue 2 (February 2018) p. 146-154.

these analyses are not qualified by the strong assumptions usually necessary to make such value judgments, leaving such determinations up to the decision makers themselves.

By contrast, MCDA attempts to deliver one integrated metric of value from multiple qualitative attributes. In this framework, various qualitative measures, criteria, and outcomes are weighted and translated into one metric that allows for a comparison of different interventions. The weights are based on value judgments and assumptions about affected parties, and depend on the goals and priorities of the decision maker.³ The quality of MCDA methods rests heavily on these decisions, and whether the assumptions are reasonable.

The QALY used in ICER's framework is an example of an MCDA that assigns weights to different health states. But the QALY does not incorporate the "other benefits and advantages" associated with the drug or device that ICER includes in its full value-based assessments, and the nature of that inclusion is not described. "Other benefits" can be substantial even if the cost per QALYs is very high, but without a clear methodology for how these benefits can be included, external reviewers cannot assess how well ICER factored them into the final analysis. Including QALY as the primary metric for comparing health states does not preclude non-health considerations, but a more transparent methodology and value weights are needed in order to assess how well the ICER value framework incorporates them.

When evaluating the effectiveness of a drug, device, or treatment, the magnitude of life improvements must be incorporated. ICER attempts to do this with the QALY metric, but the QALY only accounts for health gains or losses from a certain drug or condition—and not utility gained or lost from these interventions. This flawed scale assumes a constant, linear improvement in utility for all patients as they move along the scale. But that assumption of linear improvement cannot be true. For most patients, the change in utility from "poor" health to "good" health is almost surely greater than the change in utility from "good" health to "excellent" health. Likewise, society may prefer to target interventions to those in "poor" health rather than devote more resources to patients in relatively good health. But ICER requires a strong, linear assumption in order to compare the relative benefits to society of competing interventions.⁴

Furthermore, comparisons across illnesses and conditions actually involve difficult "apples to oranges" comparisons, and may not fully capture the benefits gained from a specific treatment or drug. In the United Kingdom, the National Institute for Health and Care Excellence recently reevaluated its QALY measures, and struggled to be analytically consistent, delaying implementation in order to reconcile its new metrics with previous findings.⁵

The QALY is a population metric, not specific to the individuals who would benefit from the treatments that ICER evaluates. This does not discredit using QALYs when considering large scale interventions that could impact a large portion of the population. But when looking at the groups

³ Charles E. Phelps, Darius N. Lakdawalla, Anirban Basu, Michael F. Drummond, Adrian Towse, and Patricia M. Danzon, "**Approaches to Aggregation and Decision Making—A Health Economics Approach: An ISPOR Special Task Force Report,**" *Value in Health*, Volume 21, Issue 2 (February 2018) p. 146-154.

⁴ Milton C. Weinstein, George Torrance, and Alistair McGuire, "**QALYs: The Basics,**" *Value in Health*, Volume 12, Supplement 1 (February 2009) p. S5-S9.

⁵ James Raftery, **A more fundamental review of QALYs is needed**, blogs.bmj.com, April 17, 2018.

that would be affected by a specific drug or device, there may not be an adequate estimate of the QALY effect in this context. According to Birch and Gafni, the incremental cost-effectiveness “ratio is a function of the total size of the programme.”⁶ This means that the “real” incremental cost-effectiveness ratio may be very different once a given treatment is implemented at different scales or in different locations. And an arbitrary threshold for the QALY, not associated with the population being evaluated, will misrepresent the effectiveness of the treatment. Therefore, using an abstracted value based on small-scale clinical evaluations to get a QALY estimate for the drug being considered may result in an incomplete and biased analysis that would not be helpful for decision-makers considering whether to cover a certain drug.

Economic Rationale Against QALYs

The QALY is an inappropriate metric on which to base an entire analysis. QALYs assume that patients are risk-neutral regarding medical interventions, which even QALY proponents admit is a strong assumption with mixed empirical support at best.⁷ Although some patients may be risk-neutral, many may be risk-averse; and assuming that patients are risk-neutral and then aggregating QALYs across society mask the more nuanced reality.

Gafni, Birch, and Mehrez argue for using healthy-years-equivalent instead of QALYs because it does not require strong assumptions about the form of patients’ utility functions.⁸ QALY proponents, however, only demonstrate that a patient “who wishes his/her decisions to be consistent with the axioms of utility theory” will have preferences that are consistent with the QALY concept.⁹ In other words, the QALY method is not based on, for example, surveys of patients’ actual preferences. Rather, researchers who use QALYs make broad assumptions about what they believe patients want from the healthcare system.¹⁰

Birch and Gafni show that the methods ICER uses do not consider the opportunity costs of new interventions and are inconsistent with welfare economic theory, which means they may lead to decisions that make the healthcare system less efficient. Sendi, Gafni, and Birch show how to use QALYs to improve the healthcare system’s efficiency, but their approach still requires the analyst to compare how resources *are* used with how they *might be* used for a new intervention.¹¹ To improve efficiency and reduce waste in the healthcare system, ICER’s analysis must consider the change in relative benefits that would come from reallocating funding away from existing interventions to those that are proven to be more effective.

⁶ Stephen Birch and Amiram Gafni, “**Cost effectiveness/utility analyses: Do current decision rules lead us to where we want to be?**” *Journal of Health Economics*, Volume 11, Issue 3 (October 1992) p. 279-296.

⁷ Milton C. Weinstein, George Torrance, and Alistair McGuire, “**QALYs: The Basics**,” *Value in Health*, Volume 12, Supplement 1 (February 2009) p. S5-S9.

⁸ Amiram Gafni, Stephen Birch and Abraham Mehrez, “**Economics, health and health economics: HYE versus QALYs**,” *Journal of Health Economics*, Volume 12, Issue 3 (October 1993) p. 325-339.

⁹ George W. Torrance, “**Utility Measurement in Healthcare: The Things I Never Got To**” *Pharmacoeconomics*, Volume 24, Issue 11 (November 2006) p. 1069-1078.

¹⁰ Stephen Birch and Amiram Gafni, “**Cost effectiveness/utility analyses: Do current decision rules lead us to where we want to be?**” *Journal of Health Economics*, Volume 11, Issue 3 (October 1992) p. 279-296.

¹¹ P. Sendi, A. Gafni and S. Birch, “**Opportunity costs and uncertainty in the economic evaluation of health care interventions**,” *Health Economics*, Volume 11, Issue 1 (January 2002) p.23-31.

Similarly, ICER's QALY method assumes that the new treatment is divisible and will exhibit constant returns to scale. That is, it assumes that the benefits per patient of a new treatment will be the same whether the program is implemented on a small or large scale, and that the program can be implemented at whatever size the decision-maker wishes without changing the incremental cost-effectiveness ratio. Such assumptions bear little resemblance to healthcare realities—some treatments may have high fixed costs or may only be cost-effective when implemented on a certain scale.

To improve the QALY metric, ICER could incorporate various measures of a cost per “life” benefit, like healthy-years-equivalents (HYE), which would offer a broader perspective of how benefits and costs are internalized with healthcare decisions. Decision-makers could then better decide whether to use or cover a particular intervention. ICER has recently updated the methodology to feature a supplementary measure called Equal Value of Life Years Gained (evLYG). ICER acknowledges that this measure “is not as flexible as the QALY in capturing benefits to quality of life but does measure any gains in length of life exactly the same across all conditions, regardless of age, severity of illness, or level of disability.”¹² A supplementary measure benefits the analysis, but we suggest including a more comparable alternative to QALY as a robustness check. HYEs capture the same idea as QALY, but under different assumptions, and the comparison between the two can assist the analysis.

Overstated Short-Term Budget Impacts

ICER's recommended price discounts for medications and devices reflect an arbitrary threshold based on economic growth instead of how insurers and patients actually purchase drugs and devices. ICER correctly notes that insurers and governments must consider short-term budget effects of paying for various drugs and medical devices, but ICER's budget figures are irrelevant. These budget impacts are based on broad, economy-wide projections and sometimes are not tied to the specific drug or device market when no price data are available. When Broder, Zambrano, and co-authors compared ICER's cost estimates to reality, they found that budget impacts for new drugs are often significantly overstated.¹³

According to ICER, “our approach favors innovation by assuming that all net health budget impact for drug spending can be allocated to new drugs alone, requiring an assumption that the background spending on existing drugs is net neutral.”¹⁴ But Birch and Gafni argue that, in order to ensure that ICER's method actually improves overall efficiency, it would need to compare any new interventions to the “highest-valued alternative use” of all existing healthcare resources, not just to the existing drugs or treatments with which the new intervention is competing. Approving treatments on the basis of whether they fall below this threshold may simply lead to more out of control spending on treatments that are not actually welfare-improving overall. Hypothetically, a proper cost-benefit analysis might reveal that the most effective strategy would be to devote part

¹² **ICER Describes for Patients and Policymakers Why the QALY Is Considered the Best Way to Reward the Care that Improves Patients' Lives**, Institute for Clinical and Economic Review press release, December 12, 2018.

¹³ Michael S. Broder, Jenelle M. Zambrano, Jackie Lee and Richard S. Marken, “**Systematic bias in predictions of new drugs' budget impact: analysis of a sample of recent US drug launches**,” *Current Medical Research and Opinion*, Volume 34, Issue 5 (May 2017) p. 765-773

¹⁴ Institute for Clinical and Economic Review, “**Overview of the ICER value assessment framework and update for 2017-2019**,” May 8, 2018.

of the healthcare budget to existing interventions and part to effective, new interventions. Complicating matters further, researchers have found that oftentimes, maximizing cost-effectiveness for individuals conflicts with maximizing cost-effectiveness for populations.¹⁵

Other Issues

Grey Literature: The current ICER policy on grey literature is too restrictive. It puts reports and findings that have not been accepted in a peer-reviewed publication at a disadvantage. But a peer-reviewed publication does not confirm the results or findings, only that the evaluation was “good enough” to enter the formal discourse. Research is an active debate. Significant findings often go unpublished, not because they lack credibility, but because they lack an appropriate journal or the author chose not to publish the results in order to pursue other research. Furthermore, it is common for multiple peer-reviewed articles and publications to publish contradictory evidence that then sparks an active debate over methodologies, data, and validity of results.

Timing of ICER Reports: ICER reviews of medical interventions sometimes occur too early in drug or device development, even coming before a consensus on the effectiveness, quality or price of the intervention. Such prematurity undermines the findings of these reports. (See Ovarian Cancer report).¹⁶ For example, ICER assumes a default cost per QALY between \$50,000 and \$150,000 when no price information is available but provides no reason for applying this assumption to the relevant target population. Nor is it clear why those assumed prices should be used, especially before any real price information is provided.¹⁷

Modeling Documentation: We do not find enough information provided in ICER reports to completely replicate or verify ICER’s results. We understand the proprietary nature of some of the analysis presented, but a simple explanation of what is ultimately multiplied, divided, added, or subtracted to reach the incremental cost effectiveness estimates would be helpful for validating results externally. Flow charts do not accurately capture the complexities involved in these sophisticated estimations. Outside researchers must know what values, data, and sources are used, or else have the methodology explained with equations and theory, in order to test the validity and authenticity of ICER’s analysis.

Intended Goal of Analysis: ICER’s goal of “bring[ing] the public directly into the critical discussions about health care and health insurance that we need to have,” lies outside the evaluation

¹⁵Attilio V. Granata and Alan Hillman, “**Competing Practice Guidelines: Using Cost-Effectiveness Analysis To Make Optimal Decisions**” *Annals of Internal Medicine*, Volume 128, Issue 1 (January 1998) p. 56-63.

¹⁶*Poly ADP-Ribose Polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value*, Institute for Clinical and Economic Review, September 28, 2017.

¹⁷The only citations given for cost per QALY bounds are the World Health Organization and American College of Cardiology. Other researchers have referred to the “murky” or “mythical” origins of the \$50,000 lower bound, which may have its origins in 1970s. Updating the QALY with more appropriate methods that account for actual patient behavior and modern innovations place the *lower* bound for the cost-per-QALY at \$109,000.

Peter J. Neumann, Joshua T. Cohen and Milton C. Weinstein, “**Updating Cost-Effectiveness—The Curious Resilience of the \$50,000-per-QALY Threshold**,” *The New England Journal of Medicine*, Volume 371, Number 9 (August 2014) p. 796-797; and Milton C. Weinstein, “**How Much Are Americans Willing to Pay for a Quality-Adjusted Life Year**,” *Medical Care*, Volume 46, Issue 4 (April 2008) p. 343-345.

of a single drug or device.¹⁸ If ICER took a more holistic approach to evaluating the healthcare system, then its reports might inform the discussions that already take place every day in academic, governmental, and social settings. Unfortunately, ICER's reports on specific treatments are too limited in scope and methodology to achieve ICER's intended goal.

Indeed, Weinstein argues that using QALYs, such as in ICER's valuation assessment, actually distracts from the public discussion about effectively allocating healthcare resources.¹⁹ According to him, ICER's methods oversimplify healthcare decision-making by ignoring resource distribution issues. Survey research shows that reasonable minds can disagree about how best to allocate scarce healthcare resources. In one study, for example, a group of researchers asked "experts in medical decision-making," potential jurors, and medical ethicists whether it would be better to screen fewer patients for colon cancer with a more effective test, or screen everyone with a less effective one.²⁰ The principles of cost-effectiveness analysis dictate that the more effective test should be used, but only 59 percent of the surveyed experts recommended that approach, compared with 44 percent of the potential jurors, and 47 percent of the medical ethicists. Such survey results suggest that ICER may not be capturing everything that matters to patients or society at-large when it comes to evaluating the costs and benefits of medical innovations. To accomplish its stated goal, ICER's framework must properly incorporate aspects of an improved life from a specific intervention so that policymakers can better decide how to use scarce resources to cover many possible interventions.

We appreciate the opportunity to comment on ICER's Value Assessment Framework. We encourage ICER to pursue a more diverse and inclusive analysis when evaluating medical interventions, and we hope that our suggestions for doing so prove helpful.

Sincerely,

Rea S. Hederman Jr.
Executive Director of the Economic Research
Center and Vice President of Policy
The Buckeye Institute

Andrew J. Kidd, Ph.D.
Economist
The Buckeye Institute

Tyler Shankel
Economic Policy Analyst
The Buckeye Institute

James B. Woodward, Ph.D.
Economic Research Analyst
The Buckeye Institute

¹⁸ Institute for Clinical and Economic Review, "**Overview of the ICER value assessment framework and update for 2017-2019**," May 8, 2018.

¹⁹ Milton C. Weinstein, "**How Much Are Americans Willing to Pay for a Quality-Adjusted Life Year**," *Medical Care*, Volume 46, Issue 4 (April 2008) p. 343-345.

²⁰ Peter A. Ubel, Michael L. DeKay, Jonathan Baron and David A. Asch, "**Cost-Effectiveness Analysis in a Setting of Budget Constraints – Is It Equitable?**," *The New England Journal of Medicine*, Volume 334, Number 18 (May 1996) p. 1174-1177.



June 10, 2019

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

Dear Dr. Pearson,

As organizations representing veterans and individuals in the military living with diverse conditions and diseases, as well as their families, caregivers and providers, we are pleased to provide feedback on the Institute for Clinical Economic Review (ICER) 2020 Value Assessment Framework.

On June 27, 2017, ICER announced an agreement to work with the Department of Veterans Affairs (VA) Pharmacy Benefits Management Services office (PBM) to support its use of ICER drug assessment reports.¹ As we understand, under this agreement, ICER is working with VA staff to integrate ICER's academic reports into the VA formulary management process of evaluating the comparative effectiveness and value of drugs. Therefore, for us, updating ICER's value framework holds particular significance due to its influence over the care that veterans and members of the military are able to access.

ICER Should Abandon the Discriminatory Quality-Adjusted Life Year and Similar Metrics

ICER utilizes a quality-adjusted life year (QALY) metric as the basis for its value assessments that is very controversial for its discriminatory impact on people with disabilities and serious chronic conditions. The QALY inherently discriminates against patients and people with disabilities by placing a lower value on their lives. In fact, in 1992, the U.S. Department of Health and Human Services denied a state waiver application after determining the use of QALYs in Medicaid would be discriminatory and potentially violate the Americans with Disabilities Act (ADA).² Also, Medicare has a statutory ban against use of QALYs and similar metrics for coverage decisions.³ We have significant concerns that similar protections against the use of a cost-per-QALY value assessment do not exist for our members. It is profoundly unfair and offensive to those who have served this country to allow for this kind of

¹ See <https://icer-review.org/announcements/va-release/>

² See <https://www.nytimes.com/1992/09/01/opinion/1-oregon-health-plan-is-unfair-to-the-disabled-659492.html>

³ 42 USC Sec 1320e, 2017. Accessed December 4, 2018.

discrimination in the veterans health system. Therefore, we urge ICER to abandon the use of the QALY in its value assessments and instead work toward more patient-centered strategies for assessing value that are not based on averages so that our veterans health system is not susceptible to this kind of discrimination.

ICER's Value Framework Should Better Reflect the Value of Treatments for Individuals

Under the existing methodology, ICER's value determinations are based on population-level averages that do not reflect individual differences among veterans. Additionally, ICER tends to conduct their value assessments at a stage when inadequate data is available to reflect subpopulations, especially veterans in particular. No veteran is average and treating them as such only undermines the clinical knowledge of providers in the veterans health system that may not yet be reflected in the research. We are concerned that the use of ICER's assessments will further limit access to care tailored to individual veterans, thereby exacerbating the existing access challenges that they and their caregivers often face. In an era when policy-makers and stakeholders want to improve care to veterans, the VA's health system should embrace patient-centeredness, as opposed to becoming entrenched in a one-size-fits-all perspective of health care value. Different people respond differently to the same drugs and no two veterans are the same or have the same health care needs. Each veteran deserves care from a health system that recognizes his or her unique needs and characteristics.

Any ICER Value Assessment Used by the VA Must Incorporate Feedback from Veterans

ICER's research is often criticized by patients for failing to incorporate their input or focus on the outcomes that matter to them. We are unaware of ICER surveying veterans for information about the outcomes that matter most to them or the goals for their treatment. Certainly, we have not been directly engaged in the development of any value assessments conducted by ICER for the VA's use in developing their formularies. Veterans have unique health challenges that cannot be averaged out alongside civilian populations. The point of a health system managed by and for veterans is to ensure that there exists an infrastructure for treating veterans with disabilities and serious chronic conditions that is responsive to their unique needs and characteristics. Without specific engagement of veterans, ICER cannot develop a value assessment that would be constructive for use by the VA to achieve outcomes that matter to veterans in the real world.

Care that Fails Veterans Leads to Higher Costs

Standardized care decisions create barriers to certain treatments for veterans that don't meet "average" thresholds, leading to increased costs when treatments fail the patient. When patients cannot access treatments that work for them, the VA system bears the cost of reduced treatment adherence, increased hospitalization and other acute care episodes, as well as the societal costs of increased disability over time. In this age of personalized medicine, we want the VA to rely on expertise that will drive the agency to reduce costs and improve care quality by better targeting treatments shown to work on patients with similar characteristics, needs and preferences, thereby avoiding the waste of valuable resources on care that veterans do not value.

In conclusion, prescription drug coverage determinations based on ICER's currently flawed analyses are not the answer and can only serve to further limit access to care for veterans with disabilities and serious chronic conditions, thereby exacerbating the challenges that they and their caregivers often face. We want ICER's value framework to be updated in a manner that would constructively assist VA to be a model for putting patients first by engaging patients. Otherwise, it is not appropriate for the VA to be referencing ICER's studies at all.

Thank you for this opportunity to comment. In light of your direct relationship with the VA, we hope that you will act on our recommendations.

American GI Forum of California

AMVETS, Department of California

California Association of County Veteran Service Officers

National Guard Association of California

Women Veterans Alliance



Headquarters:
734 15th Street NW, Suite 300, Washington DC 20005
202.659.9709 Phone 202.974.7999 Fax

Denver Office:
1355 S. Colorado Blvd., C-601, Denver, CO 80222
1-888-234-2468 Phone 202.974.7999 Fax

New York City Office:
165 West 46th Street, Suite 805, New York, NY 10036
917.305.1200 Phone 212.967-8717 Fax

Research & Training Institute:
520 Walnut Street, Philadelphia, PA 19106
267.295.3000 Phone 215.883.2580 Fax

June 10, 2019

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

Re: Institute for Clinical and Economic Review - Public Input for 2020 Value Assessment Framework

Dear Dr. Pearson,

On behalf of the Cancer Support Community (CSC), an international nonprofit organization that provides support, education, and hope to people impacted by cancer, we appreciate the opportunity to respond to the request for public input for the Institute for Clinical and Economic Review's (ICER) 2020 Value Assessment Framework. As the largest direct provider of social and emotional support services for people impacted by cancer, and the largest nonprofit employer of psychosocial oncology professionals in the United States, CSC has a unique understanding of the cancer patient experience. Each year, CSC serves more than one million people affected by cancer through its network of over 45 licensed affiliates, more than 170 satellite locations, and a dynamic online community of individuals receiving social support services. Overall, we deliver more than \$50 million in free, personalized services each year to individuals and families affected by cancer nationwide and internationally.

Additionally, CSC is home to the Research and Training Institute (RTI)—the only entity of its kind focused solely on the experiences of cancer patients and their loved ones. The RTI has contributed to the evidence base regarding the cancer patient experience through its Cancer Experience Registry, various publications and peer-reviewed studies on distress screening, and the psychosocial impact of cancer, and cancer survivorship. This combination of direct services and research uniquely positions CSC to provide valuable patient and evidence-informed feedback on ICER's value assessment frameworks.

We recognize the efforts that ICER has taken to better include patients and incorporate patient feedback. We have worked with ICER to ensure that the cancer patient voice is heard and understood and we are appreciative of the outreach offered by ICER staff. Yet, there is much more to be done. In the patient engagement guide, ICER states that their core mission is to "produce information that helps stimulate dialogue on how to achieve fair pricing, fair access, and future innovation." As such, it is critical for ICER to understand the potential implications of their assessment for patient access. Value assessments influence the ability of patients to access

the most appropriate therapies. As these therapies can improve quality of life, extend survival, or prove lifesaving, we believe that patients must truly be at the center of your work.

We respectfully submit the following comments and look forward to the opportunity to engage in future discussions for the purpose of securing a healthcare system that provides sustainable access to both high-quality and high-value care for all patients.

Sustainable Access to High-Value Care for All Patients

The stated goal of ICER's value assessment framework is to help the United States evolve toward a health care system that provides "sustainable access to high-value care for all patients." ICER calculates incremental cost effectiveness from the health system perspective. Specifically, ICER applies two distinct elements - namely *Long-Term Value for Money* and *Short-Term Affordability* - to derive high-value care for all patients. Cost-effectiveness from the health system perspective is one endpoint, but cannot be the primary driver to determine high-value care for *all* patients.

As noted by CSC in previous comments, it is critical to clearly delineate the difference between the concept of "value" as it pertains to medical treatments and devices compared to an assessment based primarily on the financial implications of those treatments and devices. The concept of value, if truly intended to provide sustainable access to high-value care for *all* patients, must be broader than cost-containment and budget impact. Patients seek care for different diseases diagnosed at different stages of progression with different states of underlying physical and mental health and with different life goals and perspectives. Given the unique physical, mental, and psychological make-up of each individual patient, there is no one-size-fits-all value framework to determine high-value care for all patients. Patients make different determinations regarding their care based on any number of variables unique to them. Therefore, we would be pleased to partner with ICER to ensure the inclusion of more real-world evidence such as that gained from our 14,000 Cancer Experience Registry participants. Our researchers can hold focus groups and conduct mixed methods research during each phase of assessment to ensure that ICER is incorporating the concepts most salient to patients living with the specific disease.

Cost Per Quality-Adjusted-Life-Year

Notwithstanding ICER's blanket statement that the cost per quality-adjusted-life-year (QALY) will continue to be the primary measure of incremental cost-effectiveness, CSC urges ICER to reject the QALY as a basis upon which to allocate resources. In 2018, CSC published a study that found that three-quarters of cancer patients did not believe that the QALY is a good way to measure value in healthcare and were concerned that decision makers were utilizing the QALY in ways that could negatively impact their access to care (Franklin et al., 2018).

Allen et al. (2017) note that the QALY may not capture the full range of components necessary for individual decision-making. The QALY only captures some of the benefits created by a health care intervention and does not always capture the full health or well-being of patients (International Society for Pharmacoeconomics and Outcomes Research, 2017). It also doesn't incorporate preferences regarding the weight given to health gain and has been criticized for

being discriminatory against certain patient groups such as people with disabilities (International Society for Pharmacoeconomics and Outcomes Research, 2017). The QALY operates from the premise that a more desirable health state is deemed more valuable (Weinstein, Torrance, & McGuire, 2009). However, Weinstein, Torrance, and McGuire (2009) state that a critical question is “value to whom?” There remain ethical, conceptual, and operational concerns regarding its use (Prieto & Sacristán, 2003).

Throughout its value assessment framework, ICER references the importance of high-quality evidence. Yet, the QALY is derived from assumptions made by individuals often lacking any experiential basis upon which to measure either the burden or the quality of life of someone confronting a particular condition, advanced age, or a disability. Furthermore, these assumptions are often inherently discriminatory and have negative consequences on the access to care for those who are ill, elderly, or living with a disability. Unlike broad stroke QALY policies based on third-party conjecture, patient-centered care delivers true high value-care for all patients.

We also do not believe that the Equal Value of Life Years Gained (evLYG) is an appropriate tool and includes many of the same challenges as the QALY. The evLYG does not account for improvement of quality of life and other important components of value. Although these types of tools have long been utilized, we support the movement to utilize more transparent, patient-centered tools such as multi criteria decision analysis.

Patient Experience Data

As mentioned above, ICER’s value assessment framework is from the health system perspective, with the two economic elements used to support this perspective being long-term value for money and short-term affordability. Despite a ‘sustainable access to high-value care for all patients’ being the ultimate identified goal, there is no mention of patients in any of the domains contributing to this goal. The domain titled “other benefits or disadvantages” appears to offer a mechanism for collecting stakeholder information. CSC recognizes and appreciates ICER’s efforts in its 2020 value assessment framework to seek stakeholder input for the next year in seven delineated potential “other benefits or disadvantages” and five delineated “contextual considerations.” However, we remain concerned that these components are included in reports after the assessment has been made. While it has been communicated to us that they play a critical role in decision making, this is not clear in the assessment reports.

CSC urges ICER to follow the lead of the U.S. Food and Drug Administration (FDA) and increase the opportunities for patients to submit valuable data and to require ICER to incorporate patient data in its efforts to better define value. The FDA has made significant inroads in requesting and incorporating patient experience data in the drug development process. Under the 21st Century Cures Act, the FDA has embarked on an aggressive plan to systematically collect and use key information about patient experiences beginning with the early phase of drug development and translation into a validated measurement set. The FDA recognizes that patients are in a unique position to contribute to an understanding of benefit and risk in the development of prescription medications, including methodological approaches to develop and identify what is most important to patients with respect to burden of disease, burden of treatment, and the benefit and risk in the management of disease. To ensure the patient experience is secured in the process, the FDA is required to issue draft and final versions of guidance documents over a five

year period. Title III of the 21st Century Cures Act is described as giving the FDA an opportunity and directive to advance the science and efficacy of medical innovation to address critical unmet needs of patients.

In conclusion, CSC's recommendations are as follows:

Value Assessment

- Limit inclusion of budget impact in the final value assessment, reporting it as just one endpoint.
- Recognize ongoing value including late and long-term benefits and effects.
- Define health system perspective as opposed to societal perspective.
- Incorporate real world evidence whenever possible and partner with patients, patient advocates, and other experts to ensure the inclusion of such evidence.
- Include the full range of health care costs and cost offsets in the final assessment.
- Measure and account for alternative systems costs or offsets—such as treatment every 3 weeks vs. once per week which allows for fewer disruptions to work, home, and family life and reduced costs as they relate to out-of-pocket expenses and transportation.
- Conduct value assessments only when adequate data are available.
- Eliminate the use of the QALY and evLYG and rely on alternative measures such as multi-criteria decision analysis.
- Ensure that “other benefits or disadvantages” and “contextual considerations” play a key role in assessments. Communicate how voting panels incorporated these concepts into their decision making.
- Organize assessment by subpopulations, to be defined with significant patient input.
- Provide not only health system perspective but also societal perspective, both of which should be informed by patient input.

Transparency

- Ensure transparency at each point of the methodological process including not only the specifics of the method but also the rationale, assumptions, and literature to support those decisions.
- Ensure transparency with all resources used in the development of evidence reports.

Revisions

- Revise assessments as new evidence becomes available (including new options for treatment both in terms of treatment types, medications available, and administration options) and previous information becomes outdated and/or reviews of past assessments on a regular basis to ensure timeliness.
- Provide transparent and specific guidance for assessment updates to reflect the evolution of scientific evidence and introduction of new treatments and devices.

Patient Input

- Partner with patient advocates at each stage of the assessment process, particularly at the beginning stages so that they may help inform assumptions and key concepts.
- Allow for a more flexible process by which patients can access all of the relevant information and apply weights that are most appropriate for their circumstances and preferences.

- Include patients and multidisciplinary experts (throughout the entire value assessment process) who have experience and knowledge of that specific disease state.
- Incorporate a specific number of diverse patient representatives who represent a broad range of voices and experiences. They should be involved at each step of the value assessment process including (but not limited to) the evidence report develop and when votes are taken.
- Allow for weights to be assigned based on user preferences and assign higher levels of value to components that are most important to patients.
- Provide patient representatives with understandable information at appropriate literacy, health literacy, and numeracy levels.
- Recognize that many stakeholders, including patients and patient advocates, do not have access to peer reviewed literature and databases. This makes it extremely challenging to provide comments that reflect the most up-to-date evidence.
- Provide ongoing education in health economics and outcomes research for patients and patient advocates.
- Describe when input was utilized and when it was discarded, and the reasons for each.
- Work to ensure that outcomes reflect patient experiences and preferences.
- Utilize existing patient registries and survey databases to explore and incorporate patient experience data.
- Include costs that are representative of the net price most relevant to the patient.

Implementation

- Understand the potential and applied use of value assessments by a variety of stakeholders regardless of intended use and audience.

Dissemination

- Work with patient advocacy groups and patients to disseminate results in a manner that is clear and understandable for all stakeholders.
- Provide clear instructions for implementation and warnings against unintended use.

In closing, thank you for the opportunity to submit these comments. We welcome the opportunity to engage in further discussions with you to ensure the patient experience is valued and all patients have access to high-quality health care. If you have questions regarding our comments, or if we can serve as a resource, please reach out to me at

Efranklin@cancersupportcommunity.org.

Sincerely,



Elizabeth F. Franklin, LGSW, ACSW
Executive Director, Cancer Policy Institute
Cancer Support Community Headquarters

References

Allen, J. D., Stewart, M. D., Roberts, S. A., & Sigal, E. V. (2017). The value of addressing

- patient preferences. *Value in Health*, 20(2), 283-285.
- DuBois, R. & Westrich, K. (2017). Value assessment frameworks: How can they meet the challenge? *Health Affairs*. Retrieved from <http://healthaffairs.org/blog/2017/03/02/value-assessment-frameworks-how-can-they-meet-the-challenge/>.
- Franklin, E. F., Nichols, H. M., Charap, E., Buzaglo, J. S., Zaleta, A. K., & House, L. (2018). Perspectives of patients with cancer on the quality-adjusted life year as a measure of value in healthcare. *Value in Health*, 22(4), pp. 474-481.
- International Society for Pharmacoeconomics and Outcomes Research. (2017). *Initiative on US value assessment frameworks. Draft special task force report, July 7, 2017. A health economics approach to U.S. value framework assessments*. Retrieved from <https://www.ispor.org/ValueAssessmentFrameworks/Docs>
- National Pharmaceutical Council. (n.d.). *Guiding practices for patient-centered value assessment*. Retrieved from <http://www.npcnow.org/guidingpractices>
- Prieto, L. & Sacristán, J. A. (2003). Problems and solutions in calculating quality adjusted life years (QALYs). *Health Quality Life Outcomes*, 1(80), 1-8.
- Weinstein, M. C., Torrance, G., & McGuire, A. (2009). QALYs: The basics. *Value in Health*, 12(1), S5-S9.



June 10, 2019

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

Submitted electronically: publiccomments@icer-review.org

Dear Dr. Pearson,

CancerCare, the leading national organization providing free professional support services and information to people with cancer, is pleased to provide feedback on ICER's 2020 Value Assessment Framework.

CancerCare has 75 years of experience assisting people with cancer and their care partners, giving us great insight into the many ways in which people with cancer experience their diagnoses, approaches to treatment, and hopes for cure versus life extension and/or disease management. Our belief in the primacy of the patients' voice has led us to undertake a multi-year initiative designed to reframe the national healthcare policy dialogue to include what is important to patients and their families, and to make sure that patients' values and priorities are incorporated into treatment decision making. CancerCare's Patient Value Initiative¹ has cemented our belief that as we continue moving toward patient-centered care, which the National Academy of Medicine has declared to be the gold standard of cancer treatment delivery,² any consideration of the value of a treatment must recognize the differences in people and their priorities.

This is why CancerCare requests that ICER discontinue its reliance on QALYs in its value assessments.

No two cancer patients are the same, so when it comes to treating cancer, any one-size-fits-all approach to covering treatment options can have life or death consequences. QALYs are well-known to discriminate against patients with chronic diseases, seniors, and people with disabilities. QALYs place greater value on years lived in full health, or on interventions that prevent loss of perfect health, while discounting gains of health for individuals with chronic illnesses. As a result of this calculation, it may be determined that people with disabilities and serious chronic conditions are not worth treating.³ For example, if a QALY methodology had been used to determine whether Jimmy Carter's use of immunotherapy was to be covered by Medicare, coverage would have been denied and surely, he would not be alive today.

The U.S. has repeatedly rejected the use of cost-effectiveness assessments and QALYs to make coverage decisions for treatments in our public programs, opting for more fair and equitable ways to make coverage decisions. In 1992, the U.S. Department of Health and Human Services rejected the state of Oregon's request to proceed with their prioritized list based on explicit cost-effectiveness ratios derived from QALYs, citing the potential for the method to discriminate against people with disabilities, which would violate the

¹ <https://www.cancercare.org/patientvaluesinitiative>

² Institute of Medicine: Delivering High-Quality CancerCare: Charting a New Course for a System in Crisis. Washington, DC: The National Academies Press; 2013, <https://www.nap.edu/catalog/18359/delivering-high-quality-cancer-care-charting-a-new-course-for>

³ See <https://www.healthaffairs.org/doi/10.1377/hblog20181025.42661/full/>



Americans with Disabilities Act.⁴ Additionally, federal statute precludes Medicare from making coverage decisions based on QALYs or similar metrics.⁵

Thresholds of cost effectiveness fail to consider important differences among patients by relying on averages to define value, but no patient is average. A recent study published by Tufts University⁶ found that fewer than one quarter of cost-effectiveness analyses accounted for even the most basic differences among patients. When coverage policies are based on cost-effectiveness calculations, accountants and actuaries make medical decisions for people with cancer, overriding individual patient-centered decisions that are based on personal needs, preferences, and their physicians' judgments.

This results in value assessments that solely reflect the interests of healthcare payers while ignoring patients, and can result in people being denied effective treatments based on formulaic determinations that their treatments are "not cost-effective."

CancerCare recommends that ICER include in its assessments ongoing input of real world evidence (RWE) from multiple sources in addition to randomized controlled trials (RCT).

While RCTs play an important role in determining safety and efficacy within the context of the regulatory process, their use does not translate well to assessing a treatment's value to patients – particularly when the treatment is new or intended to treat a rare condition.

Further, since RCTs by design look at small homogenous subpopulations, their results do not carry the same level of validity when applied to a larger population of patients with diverse physical and genetic characteristics, backgrounds, social determinants of health, comorbidities, etc. Nor do they reflect differences in the various ways in which clinicians and their patients might use the treatment.

CancerCare urges ICER to give equal weight to the use of real world evidence (RWE) generated through routine patient care. As described in a recent article in *Medium*,⁷ "circumstances in which observational studies and RWE are particularly valuable include when:

- Evidence regarding the safety or efficacy of a treatment in a broader, non-target population is required
- Assessing the safety and efficacy of products that have received accelerated and conditional regulatory approval based on limited data
- Large studies are needed in order to assess infrequent events or long-term effects of a treatment
- Studying rare diseases or other conditions that are difficult to study in RCTs
- Adherence might have an impact on the treatment outcome
- A prompt result is needed
- When multiple treatment solutions are available
- Exploring population subsets such as patients with multiple comorbidities or ethnic minorities"

⁴ See <https://www.nytimes.com/1992/09/01/opinion/1-oregon-health-plan-is-unfair-to-the-disabled-659492.html>

⁵ 111th Congress of the United States of America. (2010). H.R. 3590 The Patient Protection and Affordable Care Act. Section 1182. Washington, DC.

⁶ T Lavalle, D Kent, et al. "Patient variability seldom assessed in cost-effectiveness studies." *Medical Decision Making*. 2018.

⁷ See <https://medium.com/@ImpetusDigital/real-world-evidence-rwe-for-regulatory-and-reimbursement-decisions-75ed0280a93d>.

RWE should come from multiple sources including patient registries, databases, surveys, chart reviews, claims data, and population-based surveys.

Incorporating these essential data poses many challenges which require time and investment to address, however, they are essential to accurately and fairly assessing the value of life saving treatments. Declaring the value of a treatment or medication without the inclusion of RWE because the collection of such evidence is too onerous results in a rush to judgement that is flawed, and for some patients, potentially fatal if they are denied access based on ICER's incomplete assessment.

CancerCare recommends that ICER more thoroughly incorporate the views and experiences of stakeholders, including people with the diseases and conditions being studied and their care partners.

No one knows better how a particular condition or disease impacts their lives than those with the condition, their care partners, and their clinical care teams. Likewise, no one will be more impacted by ICER's value assessment than these people, which is why their voices must be heard and given an equal vote in all value assessments. Disregarding the opinions and experiences of the very real people impacted by the medical condition addressed by the treatment being assessed creates a fatally flawed basis for any value determination.

Finally, CancerCare recommends that ICER's value frameworks be developed using transparent processes and open source methods.

To date, ICER has not shared all of its assumptions, inputs, or other critical elements with stakeholders, researchers, or the public. Without having access to this information, it is impossible to know the basis of a value assessment and thus, cannot be analyzed or evaluated by others.

If stakeholders are to play a meaningful role in assessing the value of a treatment – which we have already stressed the need for – they must have access to thorough, precise, and understandable information on inputs and methodology as well as appropriate timeframes in which to provide their input.

We appreciate the opportunity to provide our recommendations and hope that ICER will listen to the voices of those whose lives are at stake in the value assessment process.

Please reach out to Ellen Sonet at esonet@cancercare.org or Carole Florman at cflorman@cancercare.org with any questions you may have.

Sincerely,



Patricia Goldsmith, CEO
CancerCare



June 10, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109

RE: Public Input for ICER 2020 Value Assessment Framework

Dear Dr. Pearson,

Thank you for the opportunity to provide input on ICER's 2020 Value Assessment Framework. I am writing on behalf of Celgene, where we believe the value of our innovative medicines should be assessed over the long term and with a clearly defined, holistic approach. We appreciate that the value assessment process – much like the drug development process – is iterative and builds on previous learnings to optimize value for patients and the health care industry; however, in our opinion, ICER's current assessment framework provides an incomplete rendering of the value of individual therapies.

At Celgene, we've developed [Patient-Centered Principles on Value Assessments](#) that are rooted in our company's approach to value as defined by the following four pillars:

- Value to patients
- Value to the health system
- Value to the economy and society
- Value to future innovation

While Celgene thinks about value broadly across these four pillars, the goal of our Patient-Centered Principles on Value Assessments is, as the name suggests, focused on patients. Ultimately, we believe value assessments should optimize access for all patients who stand to benefit from a specific treatment. Innovative therapies are helping people live longer, healthier lives than ever before. New targeted cancer medicines are limiting cancer growth, reducing tumor size and extending overall survival.¹ Value assessments should serve to enhance access to these therapies, not serve as an impediment to treatment.



Given its potential impact on patients' access to treatment in the United States, we believe it is vital that the ICER 2020 Value Assessment Framework be revised with the following three principles in mind.

First, **value assessments should be patient-centered**. ICER's framework should measure patient-relevant outcomes and account for varying treatment responses as well as patient preferences, needs and values. To do this, ICER's framework should allow for patients, caregivers, disease experts and others to play an active role in defining and validating the assessed outcomes. Additionally, the process should be carried out in a timely and consistent manner to ensure an appropriate representation of experience and needs. Those conducting value assessments should have a formal and transparent process for engaging with a range of appropriate stakeholders, and they should promote open dialogue and ensure stakeholder perspectives are accounted for in the final assessment or decision.

Next, **value assessments should be multi-dimensional** and consider value to patients, health systems, society and the economy, and future innovation. Value is multi-dimensional and therefore any framework that seeks to assess value must be able to appropriately account for benefits that accrue to the patient, in terms of clinical benefit and improvement in quality of life or other patient-relevant outcomes; the health system, including the long-term impact on resources and budgets; society and the economy, including patient productivity, caregiver quality of life, and economic burden; and future innovation, particularly the long-term viability of the R&D ecosystem.

In order to carry out these multi-dimensional assessments, assessment bodies like ICER should utilize a broad range of relevant and reliable evidence to capture the full spectrum of value. Evidence should not just be limited to the randomized control trial, but should also include other rigorous types of evidence, data sources and methodologies, all of which are critical for developing a more complete understanding of the ways a particular treatment adds value. Depending on the timing of the assessment within a product's life cycle, different types of evidence and data may be appropriate, such as clinical studies, patient-reported outcomes, real-world evidence and health economic data. Other methodologies including systematic literature reviews, meta-analyses, indirect treatment comparisons and comparative effectiveness should also be considered, as long as they are high-quality.

ICER's framework should appropriately account for disease- and product-specific factors in the appraisal of a therapy. Factors such as the physical, emotional, social and psychological effects of a disease are important to patients and should therefore be factored into any assessment of value. A broad definition of unmet need should also be applied, including available treatment



options, treatment practices, outcomes associated with alternative interventions, resource use and access issues. Similarly, product-specific factors should be considered to better recognize the complexity of innovative specialty medicines and the inherent challenges in evidence development for rare diseases.

Lastly, **value assessments should yield timely, high-quality outputs through flexible and transparent processes.** The field of medical innovation moves quickly, so it is imperative that ICER's assessments are delivered in a timely manner that facilitates patient access to new treatments, but also flexible enough to account for emerging data and evolving perspectives. To do this, assessment bodies such as ICER should ensure they have the resources and capabilities necessary to expediently evaluate a broad range of evidence and methodologies.

ICER's framework should guarantee transparency throughout the assessment process and its subsequent outputs. The process should be explicitly and clearly laid out in guidelines and should promote ongoing communication and engagement that is patient-centered, solutions-oriented and includes the opportunity for appeal. Furthermore, we encourage ICER to increase its level of transparency by making all aspects of its methodology available to the public. Enabling reproducible results will foster collaboration with other stakeholders and increase ICER's overall credibility.

Our commitment to value and innovation is stronger than ever—from our recently released [2019 Value and Innovation Report](#), to our [Principles for the Pricing of Innovative Medicines](#), to our [Value Hub](#). We have underscored that commitment by reinvesting an industry-leading 39% of our revenue in R&D over the last five years.^{2,3} Not only are we the highest-ranked biopharmaceutical company in terms of R&D intensity, but we are number three globally across all industrial sectors.⁴

Value is a cornerstone for Celgene. We strongly believe that our continued commitment to R&D has yielded immense benefits for patients, the health system, society and the economy, and to future innovation. We encourage ICER to develop a framework that recognizes the wide-ranging value of innovative medicines and further strengthens our R&D ecosystem for patients.

Sincerely,

A handwritten signature in black ink that reads 'Richard H. Bagger'.

Richard H. Bagger

Executive Vice President, Corporate Affairs & Market Access



¹ Bazzani R, Bhandari A, Cariola P, et al. Global oncology trends. IQVIA Institute for Human Data Science. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-oncologytrends-2018.pdf?_=1550213674665. Published May 2018. Accessed April 9, 2019.

² Numbers based on Generally Accepted Accounting Principles (GAAP) from Celgene Data on File.

³ Florko N. A new study sparks a war of words over the drug industry's commitment to research. STAT.

<https://www.statnews.com/2019/05/14/war-of-words-over-pharma-commitment-to-research/>.

Published May14, 2019. Accessed May 21, 2019.

⁴ Hernández H, Grassano N, Tübke A, Potters L, Gkotsis P, Vezzani A. The 2018 EU industrial R&D investment scoreboard. European Commission – Joint Research Centre. 2018. doi:10.2760/131813.



COMMUNITY ONCOLOGY ALLIANCE
Innovating and Advocating for Community Cancer Care

1225 New York Avenue, NW, Suite 600
Washington, DC 20005
(202) 729-8147 | communityoncology.org

President
Michael Diaz, MD
Florida

Vice President
Kashyap Patel, MD
South Carolina

Secretary
Miriam J. Atkins, MD, FACP
Georgia

Treasurer
Ricky Newton, CPA
Virginia

Executive Director
Ted Okon
Washington, DC

Directors
Lakshmi Aggarwal, MD
Indiana

Robert Baird, Jr., RN
Ohio

Harry (Mac) Barnes, MD
Alabama

Edward (Randy) Broun, MD
Ohio

Steve D'Amato, R. Ph., BSPharm
Maine

Marsha DeVita, NP, AOCN
New York

Stephen (Fred) Divers, MD
Arkansas

Chancellor Donald, MD
Louisiana

David Eagle, MD
North Carolina

Stuart Genschaw
Michigan

Lucio Gordan, MD
Florida

Bruce Gould, MD
Georgia

Edwin Graham
New York

Robert Green, MD
New York

Anshu Jain, MD
Kentucky

Terrill Jordan
New Jersey

Dinesh Kapur, MD
Connecticut

Edward Licitra, MD
New Jersey

Joseph Lynch, MD
Pennsylvania

Barbara L. McAneny, MD
New Mexico

Mark Nelson, PharmD
Washington

Todd O'Connell
New York

Kathy Oubre, MS
Louisiana

Debra Patt, MD
Texas

Jeff Patton, MD
Tennessee

William (Bud) Pierce, MD
Oregon

Marissa Rivera, MBA
Oregon

Barry Russo
Texas

Jeff Vacirca, MD
New York

Seaborn (Donny) Wade, MD
Virginia

June 7, 2019

Institute for Clinical and Economic Review
Two Liberty Square
Ninth Floor
Boston, MA 02109

On behalf of the Board of Directors of the Community Oncology Alliance (COA), I would like to thank you for inviting the Community Oncology Alliance (COA) to provide suggestions for the 2020 Patient Guide of the ICER Value Assessment Framework. COA welcomes the opportunity for meaningful collaboration as ICER seeks to shape and improve its value guidelines.

For more than 16 years, COA has built a national grassroots network of community oncology practices who have come together to advocate for public policies that benefit the patients with cancer we serve. COA initiatives support all aspects of the cancer care delivery team, including oncologists/hematologists, pharmacists, mid-level providers, oncology nurses, patients, survivors, and caregivers. This involvement has extended to life science companies, as well as federal, state, and regional payers, employers, employer health groups, and others that impact this delivery system.

COA has an extensive track record of envisioning a cancer care system that is oriented to provide patients with quality, affordable cancer care close to where they live and work. We guided the formation of the first accredited Oncology Medical Home (OMH) program in 2014, which started with a historic gathering of payers, cancer advocacy groups, providers, administrators, and other champions to formalize the first set of quality and value measures for cancer care. This effort has catalyzed the promotion and support of various payment reform models for cancer care across the country. COA has currently identified 20 such active models, all of which are different and unique. Because of that, COA has also been strategic in identifying best practices within these models that might be shared with others.

Since its inception in 2005, ICER has grown in prominence and influence in the health care community. ICER's evidence reports evaluating the "value" of drugs and treatments are increasingly being cited by payers and stakeholders in their decisions surrounding payment and access. Practically speaking, this means patient access – or lack of access – to critically needed, groundbreaking cancer treatments is being increasingly influenced by ICER recommendations. As such, we feel that COA's perspective as a leader in cancer care, oncology payment and delivery reform, and stakeholder cross-collaboration is an important addition to the ICER process. Unfortunately, given the short nature of the comment period and late notice of it, COA's comments on these issues are forced to be brief. We hope that ICER will continue to have an open and honest dialogue on these issues with more opportunity for input in shaping the value framework.

The remainder of this document will be used to relay findings, lessons learned, and suggestions that COA believes may be useful to ICER in the further development of a universally accepted value framework.

Current Landscape of Value in Oncology

As mentioned, COA has identified at least 20 oncology payment reform models in cancer care that are currently active in the United States' health care marketplace. Recently, payment models are predominantly developing at regional levels with the self-insured employer community. The goals, strategies, and missions of these models are more focused on the employee who is a cancer survivor. The emphasis has been on cost with respect to services (value), site of care differentials, access issues, communication, collaboration and coordination, as well as general support.

These existing, active models that are driven by employers reflect a view of value that differs from other stakeholders. The emphasis on the employee who is a survivor requires a new approach, understanding, and set of skills. When done properly, these employer-driven reform models are growing in both number and scope and the base of participating employers is also growing. ICER could be a valuable resource to this evolving group of decision makers for high quality and value in health care.

The dominant oncology payment reform effort today is the Centers of Medicare & Medicaid Innovation (CMMI) Oncology Care Model (OCM). The OCM is the first CMMI specialty care model and serves approximately 35 percent of all Medicare beneficiaries with cancer. COA has provided significant support to approximately 80 percent of the participants in the OCM since its inception, and much of it is based on the Oncology Medical Home work that COA has led.

The impact of the OCM has been transformative; however, it has struggled in many areas. Based on qualitative and quantitative feedback COA has gathered, the primary issues affecting its success are the complexity and communications and timing delays in this model. The payment methodology within this model has many opaque multipliers and participants are challenging the end financial projections. While some reports indicate substantial improvements, these reports are not aligning with the expected performance-based payments. One of the main explanations for this disparity relates to how value in the OCM is measured between existing and new/novel therapies.

There are many lessons to promote value in cancer care that can be learned through the OCM and other oncology payment reform models that COA has observed. These will be addressed in the "Guidance" section to follow.

Guidance:

Community oncologists are concerned about the escalating prices and costs of cancer drugs, as well as the overall increasing total cost of cancer care. As leaders in the delivery of cancer care, we are mindful of our responsibility to be good stewards of costs we can control, including the utilization of drugs and services.

Much has been said regarding the drivers to the costs of cancer drugs and treatments. Although some of these impediments are being addressed, no true standard exists on how the price of a drug, or service, is being weighed against its benefit. For example, drug costs are typically viewed as a standalone metric with minimal regard to other costs that are being avoided, such as side effects, missed work hours, caregiver needs, and

more. COA commends ICER for undertaking the challenge of viewing drug value in its entirety and “*translating evidence into policy decisions that lead to a more effective, efficient, and just health care system.*” This sets the stage for a functional, universal, and practical model that manufacturers and provider teams can use to prove the value of a drug or service – and before ICER evaluates these products.

COA has researched and discussed value statements and missions of some of the leading cancer therapy companies. Each and every one of these companies has a value assessment tool in use. However, there is minimal consistency between the processes employed by these companies and how they process metrics in the evaluation of value. The optimal goal would be a standard methodology, using existing evidence, that would promote a standard, patient friendly, easy-to-understand template to define this value. COA is prepared and interested in assisting ICER in such an endeavor. The following sections are organized by category, with details under each section.

Defining Fundamentals of Value:

A) Patient friendly: Patients with cancer are, in many ways, the victims within our health care delivery system. This is particularly true for cancer. The term financial toxicity was born out of unexpected financial hardships. Some of these hardships could be prevented if the patient was better informed and more involved in the care process. Focusing on the patient for value discussions will require different strategies and a new vocabulary. There are countless examples of patient communication techniques that were used in the OCM. Many of these techniques failed due to their inability to communicate effectively with patients with cancer. Trust becomes a key ingredient in effective patient guidance and support through care improvement efforts. It fosters a common language that is shared between care teams, manufacturers, and other supportive entities.

- *We encourage ICER to ensure that patients are the focus of all definitions of value and that their firsthand input is both encouraged and accepted.*

B) Compare total costs of care: Once a comprehensive, functional model is created for value it should be used for comparative analysis. Science is changing rapidly. This has been most evident in cancer care with the introduction of immune-oncology and cellular therapeutic agents. On the surface it would appear that these classes of drugs are incredibly expensive. However, when these new therapies, and the attendant annualized total cost of care, are compared to traditional care, the total annual cost is not as high. This is due to the reduced dependence on costly supportive care, lower risk of adverse events and hospitalizations, and improved progression free and increasingly overall survival. This will only be understood if new therapies are compared to historical treatments with all inputs considered. Creating a total, comparative picture promotes greater understanding of the total cost of care.

- *We encourage ICER to ensure that the definition of value weights the total historic cost of care against new treatments or therapies.*

C) Transparency: The lack of transparency has worked against some of the reform models – including the OCM. Explanations on why, or why not, a drug or therapy provides value should be clear, evidenced-based, and reproducible. Graphics and other information regarding the value of a certain drug should be easily understood. Teams that represent and impact value need clear communication that can be used in conversations with care team managers. These managers will then be able to understand the value positions well enough that they can share and explain the same document with

their care teams AND patients, as applicable. Patients should be able to interpret the information without requiring detailed explanations of abbreviations, methodology, and metrics.

- *We encourage ICER to ensure complete transparency and communication in the definition of value.*

D) Effective communications: The most successful reform models have routine and clear lines of communications with participating cancer care teams and beneficiaries. Although this sounds elementary, and even to be expected, the lack of effective communications has hindered participation, enthusiasm, and support of reform models. Those models that have been successful have open lines of communication for questions, feedback, suggestions, etc. This thoughtful approach facilitates improvements that are implemented efficiently. The same applies to their reporting and other updates.

- *We encourage ICER to ensure effective and helpful communications as value positions are developed and shared.*

Unique Nature of “Value” in Cancer Care:

A) Broader than a single episode: The majority of all active oncology reform models are typically evaluating costs and quality in six-month episodes. This is a marked improvement from viewing this information at the event or cycle level. However, there is some momentum building to view care for a full year. This perspective is more comprehensive and facilitates annual budgeting which should prove helpful for actuaries involved in predicting costs.

- *We encourage ICER to reflect the cost of a therapy for a minimal duration of 6-12 months.*

B) Beyond the individual treatment only: Therapies are changing rapidly. Traditional therapies included a sequenced list of supportive drugs before, during, or after the anti-cancer agent. These additional drugs add to the cost of the cancer treatment. These expenses increased further when uncontrolled toxicities prompted emergency room visits and hospitalizations. The OCM has made some progress in encouraging the calculation and communication of total cost of care in treatment plans but doing so has not necessarily been easy or correct.

- *We encourage ICER to ensure that related costs are included in the total cost of care calculations that inform value decisions.*

C) Accounting for all that are touched by cancer: Other stakeholder groups are now more active in reshaping health care delivery systems. Their interests and goals are often more patient-centric than most prior innovations. These groups include employers, employer health groups, patient advocacy groups, and insurance benefit advisers. Oftentimes, they are emphasizing site of care differences, access issues, value-based insurance design (VBID), improved coordination of care, and timely delivery of care or therapy. These entities have demonstrated their understanding of the complications and misalignment of incentives that are plaguing the attainment of quality and value-based cancer care. Ongoing dialogue and working relationships with these groups have been incredibly helpful in guiding COA’s efforts to make real improvements in cancer care.

- *We encourage ICER to include stakeholders from all of these groups in the continued development of sound guidance in defining value.*

- D) Defined end goals:** There has been much debate on the *best* measure of value in cancer care. Is it Overall Survival (OS) or Progression Free Survival (PFS)? Is it something else that includes both? The OS advocates are champions for extended life, regardless of the costs. Costs could potentially increase up until time of death when measuring OS. PFS advocates argue that PFS translates to a stable disease and potentially a cure. The PFS camp argues that treatment has not intensified and therefore the costs would also be stabilized. COA has come to understand that drug companies will emphasize one over the other based on the goals and documentation within the clinical trials for the product. This position is obvious within the product's package insert. This messaging is consistent for that product and after the launch of that product. This inconsistency can prove challenging as we work together to evolve towards a standard measurement.
- *We encourage ICER to understand the unique nature of cancer, consider all measures of value in this disease, and align them for consistency.*

The Multi-Stakeholders Perspectives:

The groups of participants that are interested in health care are more diverse than ever. These different groups are seeking reputable information and guidance related to quality and value in health care. This is particularly true in cancer care. Each has their own unique vocabulary and questions in pursuit of the better care. The below explores each of these groups. *COA believes that ICER's mission should include communication processes that are focused on each of these groups, and that their firsthand input be sought for any value reports undertaken in the oncology arena.*

- A) Patients:** Patients typically seek insights and opinions from individuals they trust. This can be their current provider, another provider that is recommended by a close friend, a family member, a co-worker, or trusted friend. Rarely does a patient or family have meaningful qualitative information to assist them with this decision.
- B) Patient groups:** The majority of patient groups focus on the cure and support for a specific disease. References for their mission and focus may come from many different sources. COA has been unable to find a consistent source of unbiased dependable information across these organizations.
- C) Care teams:** Oncology care teams have minimal information to guide them through the evolving emphasis of quality and value in cancer care. Although there is a vast library of tools and resources to assist with quality, there is much less evidence regarding value. There is even less trusted information on how these teams compare against their peers in the delivery of value. There have been some national attempts in this area, but the complexity of these attempts has overshadowed potential benefits.
- D) Payers:** Payer stakeholders of all shapes and sizes are demonstrating attention in these areas and some have implemented their own quality and value models. Unfortunately, patients and providers are not always included in the designs of these models. The payers' emphasis on tactics such as pharmacy benefit managers (PBMs), "fail first" step therapy policies, and secretive negotiated discounts with drug manufacturers, is working counter to the pursuit of transparent definitions of quality and value by others.

- E) **Employers:** Medium and large employers, both regional and national, who are self-insured are driving the more impactful reform models for cancer care. Their newfound education and understanding of misaligned incentives in health care are prompting radical changes in health care benefits designs and employee support systems. They are also in need of trusted and updated information that will support these continued changes. COA has recognized the importance of employers in patient-centered reform and is partnering with them directly in several markets to drive these efforts forward, toward success.
- F) **Employer health groups and coalitions:** Over the last 10-15 years, employer health groups and coalitions have become critical leaders in educating employers on value-based health care, opportunities to get engaged, and new initiatives. Their recent focus has been on the uncontrolled rising costs of drugs and treatments, as well as the site of care in which they are delivered. COA has routine discussions with these organizations and greatly respects their efforts.

Consider the Entire Cancer Journey

As mentioned above, measuring quality and value has evolved beyond a single treatment or cycle of treatments. Patients and caregivers are pursuing improvements in all aspects of the cancer care journey. Although ICER is not active in all of these phases, each are important to a comprehensive approach to quality and value. Lapses in any of the areas described below may have an adverse effect on the objectives of any quality or value-centered plan.

- A) **Pre-journey information:** The OCM emphasized the importance of structured communications to the patient and family before they began their cancer care journey. Information that is shared with the patient discusses expectations during and after treatment. The expectations are for the care team, the patient, and their family. Items that were discussed had a direct effect on how quality and value could be maximized for that specific journey. This information includes instructions on how the patient could support those goals.
- B) **Delivery of the care:** Many studies have produced findings regarding the processes used in care delivery. Processes that are chosen sometimes work to negate optimal achievement of quality and value. Some of these include site of care, timely access to oral drugs, and how adverse events are addressed. One of the challenges in health care reform is to identify and address these challenges effectively.
- C) **Improved end-of-life care:** Much has been discussed and debated regarding the decisions and timing of appropriate end-of-life care. Drug manufacturers are also confronting these same challenges as they measure OS versus PFS, and how to balance the value of those. That said, COA has heard troubling anecdotal reports of value-based efforts pre-emptively diverting patients with fully treatable and curable cancers to hospice without the input of trained oncologists. This is obviously horrific, immoral, and unacceptable. Patients with cancer and other life-threatening diseases should be given a chance to receive second opinions from trained physicians and all treatment options available when the evidence indicates the chance for survival is real. COA's hope is that the country will continue a dialogue about how we can best balance end-of-life care, hospice, and the accompanying costs with our definitions of value.

Conclusion

COA's unwavering commitment and steadfast determination to continually improve our cancer care system is driven by a mission to ensure that patients with cancer continue to have access to the highest quality, most affordable, and most accessible cancer care in the communities where they live and work.

COA appreciates ICER's efforts to better define and assess value. The U.S. health care system, and all of the industries that are touched by it, are in desperate need of a reputable source of information and guidance in this new era. As we noted earlier in this letter, given the abbreviated nature of the comment period and our late notice of it, unfortunately, COA's comments on these issues have had to be relatively brief.

We welcome the opportunity to work closely with ICER to advance meaningful, patient-centered, and value-driven policies relating to cancer care. We are available to discuss any of our concerns and recommendations provided in this letter.

We look forward to discussing these issues in greater detail with you and the ICER team.

Sincerely,



Michael Diaz, MD
President



Ted Okon
Executive Director



June 7, 2019

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

Dr. Pearson,

On behalf of the 30,000 people living with cystic fibrosis (CF) in the United States, we appreciate the opportunity to comment on the next iteration of the Institute for Clinical and Economic Review (ICER) value assessment framework. Having participated in ICER's review of CFTR modulators, we believe our insights and suggestions will be helpful as ICER's work continues to evolve.

The mission of the Cystic Fibrosis Foundation is to find a cure for all people with CF and ensure access to high-quality, specialized care. Incredible progress has been made toward this goal, particularly with the availability of modulator treatments in 2012. However, patient affordability and system sustainability are major concerns for the CF community. A treatment or cure that patients cannot afford is not effective. We appreciate ICER's efforts to provide a tool for health care system leaders to have conversations about value. We believe significant changes must be made to improve the review process and put forward the following recommendations.

Incorporating the Patient Perspective

We recommend ICER expand on current patient engagement efforts by creating a more standardized, transparent process for patients and patient organizations to contribute throughout the review process. While ICER's Patient Participation Guide and review-specific web pages provide a centralized location for input and a clear timeline for each review, patient organizations can and do provide much more input throughout drug reviews to ensure reviewers understand disease fundamentals, current treatment options, and much more.

Even for well-resourced organizations, like the CF Foundation, with the capacity to track ICER's work and engage early during the review process, it takes a tremendous amount of time, staffing, and inquiry to determine how patient organizations can be helpful, what data and expertise we can contribute, and what connections we can make to disease experts and individuals living with the disease. In our experience, we appreciated the various ways in which ICER welcomed CFF's contributions but noted that the lack of a standardized approach could bias the input process.

In the next iteration of the value framework, especially for treatments for ultra-rare diseases, ICER should more clearly define when, how, and what patient organizations can contribute. Specific examples of valuable contributions, such as patient surveys, names of individuals impacted by treatments under review, registry data, white and gray literature expanding on

disease fundamentals and current treatments, should be clearly outlined. As you know, there is tremendous variability in the size, organizational structure, capacity, and available resources among patient organizations – yet all may have something to contribute to the review process. It is incumbent upon ICER to reach out to stakeholders early to ensure appropriate and diverse input so that reviewers thoroughly understand the disease and treatments under review.

Clarity on Use and Development of Additional Data

As noted during the review of CFTR modulators and others, ICER's assessments are limited by the existence and rigor of data available at the time of review. This constraint, while understandable, is one ICER has deemed acceptable by virtue of scheduling assessments as close to treatments coming to market as possible. However, the current assessment process incorporates very limited patient-relevant information such as real-world evidence, patient experience, and patient survey data. Assessments therefore undervalue long-term benefits and outcomes that reflect patient daily living.

As a leader in U.S. health technology assessments, ICER is responsible for pushing the field forward. Many patient organizations are willing to invest in patient-centered research. ICER should provide specific guidance on patient-generated evidence including what information is valuable, what constitutes a suitable study design, whether peer-review is necessary, and how the information will be used during the assessment.

Again, we appreciate your commitment to continuous improvement of the value assessment framework. We hope our comments are helpful and, as ever, welcome any additional questions.

Respectfully,

A handwritten signature in black ink, appearing to read 'Mary Dwight', with a stylized, flowing script.

Mary Dwight
Senior Vice President, Policy & Advocacy
Cystic Fibrosis Foundation

June 10, 2019

Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, Massachusetts 02109

Re: Public input on the ICER 2020 Value Assessment Framework

Dear ICER Review Panel:

Genentech appreciates the opportunity to provide input into the ongoing development of the 2020 Value Assessment Framework. We believe there are opportunities to bring long-term, system-wide solutions that can lower costs for patients while also sustaining innovation and ensuring patients have access to the life-changing medicines that they need. Since 2016, Genentech has been an active partner in 15 unique initiatives led by ICER that span across drug-specific reviews to diverse policy topics. We provide these comments based on our deep experience with ICER and hope our suggestions contribute to a value framework that better represents multiple decision contexts and perspectives.

The measurement of value is best informed by all available evidence and its impact to a broad base of stakeholders, with patients at the center. There is no singular view or consensus among stakeholders about the value of a treatment. ICER has made meaningful changes to its value framework over the last several years. However, we remain concerned that ICER's framework does not adequately reflect the value of novel interventions to patients, providers, and payers. We provide several recommendations based on the following key themes:

1. Real-world evidence (RWE) should be formally evaluated and incorporated into the assessment of value to best account for all available evidence.
2. Economic analyses should be broadened beyond cost-effectiveness analyses (CEA), adaptable, and relevant to various stakeholder perspectives and disease states.
3. Additional potential benefits and considerations should be quantified and discussed along with other results from the report.
4. The process of ICER's value framework assessment needs to be more transparent.

1. RWE should be formally evaluated and incorporated into the assessment of value to best account for all available evidence.

RWE plays an important role in informing patient, health care provider, and payer decisions. Therefore, it should be incorporated into any value assessment of a health care intervention. The appetite for RWE is growing, with many stakeholders now leveraging it to reduce the uncertainty about interventions' long-term risks and benefits, and to better understand the magnitude of net health benefit in a patient population beyond clinical trials.¹⁻⁴ Although ICER's current framework includes real-world studies, the studies have not been evaluated and fully incorporated into the assessment of value. Of the 27 ICER assessments published since 2014, only 12 assessments discussed RWE, and nearly half of all real-world

studies were not referenced or discussed beyond their inclusion as a relevant study from the systematic literature review.⁵ By not sufficiently incorporating RWE, ICER is misaligned with how stakeholders currently assess evidence and make decisions, thereby reducing the relevance and utility of the ICER reports. By adapting the framework to better incorporate RWE, ICER can more accurately represent the evidence base of interventions and comprehensively assess their value.

1.1. RWE can augment clinical comparative effectiveness and CEA.

RWE can better inform the clinical comparative effectiveness rating and the long-term cost-effectiveness model. For products that have been on the market for an extensive length of time, RWE make meaningful contributions to reducing uncertainty and demonstrating benefits that extend beyond trial settings. This evidence should inform the ICER evidence rating, supplementing the evidence from clinical trials, to more comprehensively capture the evidence base of each intervention. By formally evaluating the evidence in accordance with best practices, ICER can assign a level of certainty and estimate the magnitude of benefit of real-world studies to incorporate into the evidence rating.

RWE can also address the uncertainty and limitations of CEA by informing scenario analyses that reflect real-world clinical practice. Clinical and economic outcomes from real-world studies would represent the cost-effectiveness rather than cost-efficacy of interventions, better addressing the needs of health care decision makers.⁶ For example, CEAs using RWE for Xolair (omalizumab) have demonstrated how data from clinical trials and real-world studies could provide a more comprehensive picture to inform decision-making. Economic outcomes from real-world studies can also supplement the results of the CEA. Incorporating and discussing these studies as a section in the report can better inform stakeholders about the economic value of interventions that may not be captured in a traditional CEA. For example, the economic benefits to the U.S. health care system of life-years gained due to the addition of an intervention would be meaningful to stakeholders, but may not necessarily be included in ICER's assessment of value.⁷

1.2. An evaluation of RWE should account for the clinical context, data source, and analytical methods.

The evaluation of RWE must be tailored for the clinical context of the review to align with frameworks and best practices for using real-world data to support decision-making.^{1, 8-11} Rather than using arbitrary criteria (e.g., N>1000 patients), an evaluation of RWE should assess if the data source is valid and reliable, as well as if the study design accounts for potential biases. For example, in rheumatoid arthritis (RA), disease-specific registries and administrative claims databases provide an opportunity to compare outcomes between treatments or treatment classes in a real-world setting.¹²⁻¹⁵ However, the market dynamics in RA allow a small number of products to hold a high percentage of market share, limiting patient access to therapies.¹⁶ As a result, real-world studies may have a smaller sample size of patients receiving individual therapies, but can still be considered high quality because they controlled for potential confounders. Formally evaluating RWE based on the data source and study design, while also accounting for the clinical context would align with how stakeholders evaluate evidence, thereby increasing the relevance, utility, and credibility of the report.

2. Economic analyses should be broadened beyond CEA, adaptable, and relevant to various stakeholder perspectives and disease states.

Information about the cost of a treatment and its benefit is undeniably important for healthcare decision-making. CEA, one of many approaches in determining cost and benefit, can be a useful approach to assessing the value of a healthcare intervention; however, it should not be the sole measure or determinant of value and value-based pricing. There is no uniformity among stakeholders about the value of a specific treatment for a specific patient. The systematic application of rigid cost-effectiveness thresholds that do not sufficiently incorporate other potential benefits of a health technology is problematic. When used, CEA should be contextualized, consensus-driven, inclusive of societal values, and supported by best practices.

2.1. CEA should reflect societal values and patient preferences.

We recommend that ICER follow best practices in the conduct of CEA by using the societal perspective as an additional base case.¹⁷ The societal perspective attempts to account for outcomes that are important to a broader set of stakeholders beyond payers. The exclusion of the societal perspective as a base case implies that it is a lower priority than the payer perspective, and that outcomes most important to patients and their families are not a priority. The Panel on Cost-Effectiveness in Health and Medicine strongly recommended that CEA incorporate the broader effects of interventions within and external to the health care sector. Specifically, the panel recommended inclusion of current and future costs paid by payers and patients; indirect costs related to patient time, transportation, and caregivers; and impact to non-healthcare sectors, such as productivity gains, social services and future consumption. The inclusion of a societal perspective as an additional base case better ensures ICER's application of best practices recommended by health economic experts; enables appropriate evaluations of their cost-effectiveness analyses against recommended and established thresholds; and allows audiences to consider results relative to other cost-effectiveness analyses conducted under similar perspectives.

2.2. CEA should be adapted to individual disease states and the body of available evidence.

The methodologic limitations of the quality-adjusted life-year (QALY), its potential to adequately account for other important benefits to patients and society, and the consequences of misuse are well-documented.^{18, 19} Therefore, it is important to tailor CEA to individual disease areas and include real-world evidence to model scenarios when available.

- The Equal Value of Life Years Gained (evLYG), which ICER has proposed to supplement the QALY, does not support a broader view of value. It is a life-years gained endpoint that excludes utility and still propagates the same underlying limitations of cost-effectiveness and cost-utility analyses.
- ICER's analyses should include additional economic endpoints to address outcomes that are important to decision makers. For example, in RA where response and remission criteria are clearly defined and assessed in most clinical development programs, a cost per response and number needed to treat for response analysis can augment the assessment of value in ways that are meaningful and interpretable for many stakeholders. The inclusion of additional endpoints would allow ICER to align with how stakeholders make decisions, improving the relevance and utility of the report.

- RWE can provide important information for scenario and subgroup analyses. Stakeholders consistently leverage RWE to inform decisions, but these studies are frequently excluded from ICER's report. Given the uncertainty and limitations associated with CEA, it is important to examine alternative scenarios and subpopulations in order to address the population-level decisions of payers and individual-level treatment decisions of patients.

2.3. Willingness-to-pay thresholds risk overriding important benefits not captured by the QALY.

Willingness-to-pay thresholds risk overriding important benefits not captured by the QALY, and as such should not be used to determine a value-based price. Should thresholds be used, there should be a recognition that there is no single threshold that represents society's willingness-to-pay for an intervention. Contemporary literature supports that the \$50,000 per QALY threshold as a qualifier of high value is arbitrary and not applicable to the current healthcare environment in the U.S.²⁰⁻²³ More recently, others have recommended increasing these thresholds to \$200,000 to \$300,000 per QALY.

2.4. ICER should continue to explore alternative measures of value to account for the pace of innovation.

The 2020 value framework is an opportunity to advance the science of value measurement and engage thought leaders active in this space. Due to the well-documented limitations of the QALY and the volume of potentially curative treatments that are expected to receive FDA approval in the near future, it is necessary and important to re-think traditional elements of health care value.^{18, 19, 24} We support the work that ICER is currently undertaking with the public and other health technology assessment agencies and encourage ICER to revisit alternatives such as the multi-criteria decision analysis (MCDA) and additional value parameters.

- MCDA has the unique advantage of bringing forth important considerations not adequately accounted for in traditional CEA and the potential to better align with societal and patient preferences. The Pharmaceutical Value Initiative (pValue) and the Innovation and Value Initiative (IVI) have initiated considerable work in the application of MCDA in the U.S. that can be leveraged for ICER's work.²⁵
- The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) defined twelve key elements for the next generation of value assessments in the U.S. Parameters that are not included in the current value framework such as the value of hope, scientific spillover, and option value can expand and improve the utility of a value assessment.^{26, 27}
- ICER can further explore extended cost-effectiveness analyses which seeks to include non-traditional health benefits such as financial risk protection, equity and distributional benefits.²⁸

2.5. Budget impact analyses should be removed from the report and disassociated with affordability judgements.

Budget impact analyses (BIA) are intended to estimate the financial consequences of an intervention based on an existing treatment mix. The utility of ICER's BIA is problematic because its national-level perspective does not address the needs of individual payers. It is further concerning that ICER provides

additional interpretation by linking BIA results to affordability based on an arbitrary budget cap. ICER has not conducted the necessary and comprehensive evaluation of factors such as willingness-to pay, tradeoffs, and values, to enable an appropriate assessment of affordability. The interpretation of budget impact analyses and resulting affordability judgements should be left to individual budget holders that reflect the U.S.' pluralistic health care system.

3. Additional potential benefits and considerations should be quantified and discussed along with other results from the report.

We share the National Health Council's view that value assessments should place patients at the center by accounting for heterogeneity in characteristics, preferences, treatment outcomes and as applicable the perspective of patients' caregivers and communities.²⁹ While ICER sought to incorporate these additional factors through their pilot during the last 2-years, the current inclusion of other benefits and contextual considerations (e.g. reduction in caregiver burden) section does not fully capture the value of interventions. A recent survey of managed care payers identified this section as the most unclear component of ICER's evidence reports.³⁰ To improve the utility of this section, we encourage ICER to explore opportunities to quantify the benefits from these domains and more robustly discuss them along with other results from the report.

To more formally quantify the weight of these potential benefits and contextual considerations, ICER should consider increasing engagements with patients and advocates. Quantifying these domains of value will allow ICER to better incorporate patient preferences into the assessment of value and inform health care decision makers about their significance. Patient surveys offer a potential method to collect patient preferences that can inform utility measures within the report. For example, the Asthma and Allergy Foundation of America's (AAFA) "My Life with Asthma" survey that was referenced in ICER's review of asthma biologics could have been leveraged to quantify factors most meaningful to patients.³¹ These elements can then be integrated as part of a net monetary benefit calculation, included as attributes in health state descriptions, or incorporated as criteria in a multicriteria decision analysis.²⁶

While ICER's current approach of qualitatively describing other domains of value provides a simpler approach, we encourage ICER to discuss these domains along with the clinical comparative-effectiveness and long-term cost-effectiveness results. By not discussing these domains of value along with the results from the other sections, ICER provides a fragmented and inaccurate assessment of value. Adding a section to synthesize the results of the clinical comparative effectiveness and long-term cost-effectiveness along with additional benefits and contextual considerations will provide additional weight to these factors and ensure that healthcare decision makers will consider these factors in their decisions.

4. The process of ICER's value framework assessment needs to be more transparent.

We appreciate ICER's actions to improve the transparency and stakeholder engagement of stakeholders. Given our extensive involvement of several ICER value framework reviews, we believe key areas in the process can be improved.

4.1. Economic models released to manufacturers should be fully executable.

We believe fully executable versions of the cost-effectiveness models should be provided to manufacturers that are included in ICER's value framework evaluations. Draft models that are currently being provided as part of the review process cannot be altered or tested. This significantly limits the utility of the model to end users and most importantly, limits the ability for public commenters to provide meaningful feedback. Additionally, the length of time for the draft model review should be extended from two to four weeks to allow sufficient time for reviewers.

4.2. ICER should increase their engagement of patients and clinicians throughout the evaluation process in order to yield more meaningful assessments.

We urge ICER to further expand and deepen the involvement of individuals who are closest to the disease areas evaluated by ICER - patients, their communities, and their clinical providers. As participants in several reviews, we find that clinical experts and patients are not fully integrated into the review process. This is further compounded by the member diversity of the Comparative Effectiveness Advisory Councils (CEPAC), who, in the majority of cases, may not have the disease-level expertise to truly appreciate the nuances and complexities of the diseases and medicines that ICER evaluates. We believe that bolstering and deepening the engagement of clinical experts and patients are amongst the most important actions that ICER can undertake.

We offer specific suggestions for ICER's consideration:

- Clinicians with expertise in the disease area of interest for ICER reports should have greater involvement in its development, extending beyond review. This involvement can include authoring report sections, choosing model inputs and being part of the evidence grading process.
- Multiple experts should be involved in order to balance the diversity of clinical opinions that frequently emerge and to prevent one individual opinion biasing the interpretation of the evidence presented in ICER reports.
- Patients should be actively included in the evaluation of the evidence and development of the report. ICER can partner with patient advocacy groups to generate evidence for the value framework assessment.
- Ad-hoc membership to the CEPAC should be extended to clinical experts and individuals with the condition that ICER is evaluating given the Council frequently lacks disease-specific expertise.

4.3. Presentation of results should be appropriately contextualized for public consumption.

Given the extensive nature of a value framework assessment by ICER, most users will consult the Report-at-a-Glance, press releases, and the executive summary of evidence reports. We believe there are opportunities to improve the communication and interpretation of results by the public:

- CEA results should be presented as ranges instead of point estimates in the report, evidence presentation, and Report-at-a-Glance

- The Report-at-a-Glance should summarize the stability of the base case estimates based on the various sensitivity or scenario analyses conducted.
- Extend the evaluation of uncertainty to ICER's value-based price recommendations by inclusion of ranges

4.4. A mechanism to assess the impact, quality and validity of value framework assessments should be established.

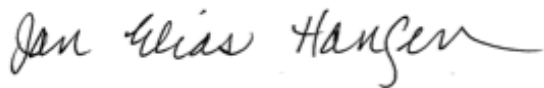
Since 2014, ICER has generated 27 assessments that are intended to inform evidence-based decision making in the health care system.⁵ As proprietors of these reports, ICER should now create a feedback mechanism on the impact of their value framework assessments. Specifically, the impact, quality and validity of findings should be evaluated once reports are released for public consumption. As the primary authors, it is ICER's responsibility to fully understand the consequences and unintended consequences of the value framework evaluations.

4.5. Updates to value framework assessments should be driven by the availability of new and meaningful evidence which extend beyond FDA approvals for new therapies.

ICER has currently established a system where evaluation updates are triggered by new therapeutic launches. As a result, the frequency of updates is variable and risks being outdated beyond a short period of time after a drug has been approved. We recommend ICER refresh reviews based on the availability of new evidence, as the reduction in uncertainty can also be as important the advent of a new treatment option.

As an organization that shares the same goal with ICER in building a more sustainable health care system, we continue to offer our expertise. Genentech welcomes the opportunity to further discuss how our recommendations can help shape ICER's iteration and improvement of the value framework assessment.

Sincerely,

A handwritten signature in black ink that reads "Jan Elias Hansen". The signature is fluid and cursive, with a long horizontal stroke at the end.

Jan Elias Hansen
Vice President, Evidence for Access Medical Unit
Genentech

References

1. U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. December 2018. Available at: <https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf>. Accessed June 7, 2019.
2. American Society of Clinical Oncology. ASCO CancerLinQ. About us. Available at: <https://cancerlinq.org/about>. Accessed June 7, 2019.
3. American Academy of Neurology. AXON Registry. About the AXON Registry. Available at: <https://www.aan.com/practice/axon-registry/>. Accessed June 7, 2019.
4. American College of Cardiology. National Cardiovascular Data Registry (NCDR). About NCDR. Available at: <https://cvquality.acc.org/NCDR-Home/about-ncdr>. Accessed June 7, 2019.
5. Drane E, Upton E, Morten P. Real-World Evidence on the Rise: Evaluating the Use of Real-World Evidence in ICER Assessments of Comparative Clinical Effectiveness. Presented at the International Society for Pharmacoeconomics and Outcomes Research Annual Meeting in New Orleans, LA; March 18-22, 2019. ISPOR PNS182.
6. Campbell JD, McQueen RB, Briggs A. The "e" in cost-effectiveness analyses. A case study of omalizumab efficacy and effectiveness for cost-effectiveness analysis evidence. *Annals of the American Thoracic Society*. 2014;11 Suppl 2:S105-11.
7. Danese MD, Reyes CM, Gleeson ML, Halperin M, Skettino SL, Mikhael J. Estimating the Population Benefits and Costs of Rituximab Therapy in the United States from 1998 to 2013 Using Real-World Data. *Medical care*. 2016;54(4):343-9.
8. Garrison LP, Jr., Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2007;10(5):326-35.
9. Hampson G, Towse A, Dreitlein WB, Henshall C, Pearson SD. Real-world evidence for coverage decisions: opportunities and challenges. *Journal of comparative effectiveness research*. 2018;7(12):1133-43.
10. Duke Margolis Center for Health Policy. A Framework for Regulatory Use of Real-World Evidence. September 2017. Available at: https://healthpolicy.duke.edu/sites/default/files/atoms/files/rwe_white_paper_2017.09.06.pdf. Accessed June 7, 2019.
11. Dreyer NA, Bryant A, Velentgas P. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness. *Journal of managed care & specialty pharmacy*. 2016;22(10):1107-13.
12. Kremer JM. The Corrona US registry of rheumatic and autoimmune diseases. *Clinical and experimental rheumatology*. 2016;34(5 Suppl 101):S96-s9.
13. Harrold LR, Reed GW, Best J, Zlotnick S, Kremer JM. Real-world Comparative Effectiveness of Tocilizumab Monotherapy vs. Tumor Necrosis Factor Inhibitors with Methotrexate in Patients with Rheumatoid Arthritis. *Rheumatology and therapy*. 2018;5(2):507-23.
14. Harrold LR, Reed GW, Solomon DH, Curtis JR, Liu M, Greenberg JD, et al. Comparative effectiveness of abatacept versus tocilizumab in rheumatoid arthritis patients with prior TNFi exposure in the US Corrona registry. *Arthritis research & therapy*. 2016;18(1):280.
15. Harrold LR, Reed GW, Magner R, Shewade A, John A, Greenberg JD, et al. Comparative effectiveness and safety of rituximab versus subsequent anti-tumor necrosis factor therapy in patients with rheumatoid arthritis with prior exposure to anti-tumor necrosis factor therapies in the United States Corrona registry. *Arthritis research & therapy*. 2015;17:256.
16. Cole A, Towse A, Segel C, Henshall C and Pearson S. Value, Access, and Incentives for Innovation: Policy Perspectives on Alternative Payment Models for Pharmaceutical Rebates. March 2019.

Available at: <https://icer-review.org/wp-content/uploads/2019/03/March-2019-ICER-OHE-White-Paper-on-Rebates-Final.pdf>. Accessed June 7, 2019.

17. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama*. 2016;316(10):1093-103.
18. Pettitt D, S R. The Limitations of QALY: A Literature Review 2016.
19. Pearson SD. Institute for Clinical and Economic Review. A Framework to Guide Payer Assessment of the Value of Medical Treatments. June 2014. Available at: <https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/>. Accessed June 7, 2019.
20. Braithwaite RS, Meltzer DO, King JT, Jr., Leslie D, Roberts MS. What does the value of modern medicine say about the \$50,000 per quality-adjusted life-year decision rule? *Medical care*. 2008;46(4):349-56.
21. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. *Medical decision making : an international journal of the Society for Medical Decision Making*. 2000;20(3):332-42.
22. Nadler E, Eckert B, Neumann PJ. Do oncologists believe new cancer drugs offer good value? *The oncologist*. 2006;11(2):90-5.
23. Seabury SA, Goldman DP, Maclean JR, Penrod JR, Lakdawalla DN. Patients value metastatic cancer therapy more highly than is typically shown through traditional estimates. *Health affairs (Project Hope)*. 2012;31(4):691-9.
24. Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies [press release]. January 15, 2019.
25. The University of Colorado Pharmaceutical Value. Complementing Coverage and Reimbursement Decisions with Multi-Criteria Decision Analysis. May 27, 2019. Available at: <https://www.ajmc.com/contributor/the-university-of-colorado-pharmaceutical-value/2019/05/complimenting-coverage-and-reimbursement-decisions-with-multicriteria-decision-analysis>. Accessed June 7, 2019.
26. Lakdawalla DN, Doshi JA, Garrison LP, Jr., Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report [3]. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2018;21(2):131-9.
27. Innovation and Value Initiative. Who We Are. Available at: <https://www.thevalueinitiative.org/who-we-are/>. Accessed June 7, 2019.
28. Verguet S, Kim JJ, Jamison DT. Extended Cost-Effectiveness Analysis for Health Policy Assessment: A Tutorial. *Pharmacoeconomics*. 2016;34(9):913-23.
29. National Health Council. The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric. March 2016. Available at: <http://www.nationalhealthcouncil.org/sites/default/files/Value-Rubric.pdf>. Accessed June 7, 2019.
30. Tennant L, Kanaskar A, Gittings K, et al. Trends in the Uptake and Impact of the Institute for Clinical and Economic Review (ICER) Value Assessment Framework (VAF) in Coverage Decisions. Presented at the International Society for Pharmacoeconomics and Outcomes Research Annual Meeting in New Orleans, LA; March 18-22, 2019. ISPOR PNS165.
31. Asthma and Allergy Foundation of America. My Life with Asthma: Survey Overview. 2017. Available at: <http://www.aafa.org/media/my-life-with-asthma-in-2017-survey-findings-report.pdf>. Accessed June 7, 2019

June 10, 2019

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

DELIVERED ELECTRONICALLY

RE: 2020 Value Assessment Framework

Dear Dr. Pearson:

On behalf of Gilead Sciences, we appreciate this opportunity to provide input into ICER's 2020 value framework update. In our comments we address the following areas:

1. The cost-effectiveness thresholds ICER uses to establish its value-based price benchmarks for treatments of both common and ultra-rare diseases;
2. The use of both the QALY and the evLYG to evaluate the degree of improvement in health outcomes;
3. 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.

Please find below our comments. We look forward to engaging in a robust dialogue on this topic.

1) COST-EFFECTIVENESS THRESHOLDS

ICER should work with other groups to individualize cost-effectiveness (C/E) thresholds, enabling greater flexibility to develop specific thresholds designed to meet the needs of individual payers, employers, providers, patients and caregivers on a case-by-case basis.

- **The healthcare payer landscape is too complex for ICER to set a national threshold.** No single C/E threshold can account for differences in patient population, unmet need, available budget and other unique challenges faced by decision-makers. To maintain a fair assessment process for all stakeholders across commercial and public segments (Medicare/Medicaid), ICER should work in developing a range of thresholds that support

a) those that are directly affected by thresholds and b) those who use these for decision-making.

- **C/E thresholds should be carefully and individually considered for any assessment and must vary according to disease, prevalence and stakeholder.** Diverse patient populations, prevalence and patient preferences are but a few examples of the extraordinary heterogeneity of disease, which confounds any attempt to apply a single threshold to all diseases and therapies. Further complexity comes from the multiple segments and subsegments in the U.S. market, including employers, payers, providers, patients, caregivers and patient advocacy groups, among others. ICER's value framework should address the significant variation observed across sub-segments of these stakeholders. So for example, a commercial payer will have variation in plans that address different needs of self-insured employers, individuals and Medicare Advantage beneficiaries, with further complexity introduced through differences in member age, disease profile, geolocation and socioeconomics. ICER should also consider incorporating processes that involve caregivers and patients to understand what is most personally relevant to these stakeholders, especially given that caregivers are also bearing the costs of disease. ICER should engage employers to understand their specific needs for their employee and family population and how specific cost-effectiveness thresholds could optimize productivity. Factors such as unmet need, breakthrough innovations, absolute health gain, end-of-life considerations and national priorities (e.g. eliminate HIV) should be factored in across all stakeholders.
- **Commonly cited thresholds, such as ICER's USD \$50,000-150,000K threshold, require greater evidence before they can be applied to new treatments.** Cost-effectiveness thresholds are arbitrary and do not reflect currently funded services through CMS or societal preferences.^{1,2} These are often derived either from other countries or are tracked to GDP estimates that have not undergone proper validation.^{3,4} Notably, Sculpher and Claxton were commissioned by NICE/NHS to review the evidence base for the QALY for England in February 2011 but were unable to support a robust evidence base.⁵ What is not widely acknowledged is that new treatments are measured without a 'ruler' or scale in which to place them into context. The use of a threshold is an attempt to take what is largely a hypothetical economic concept in which there are extensive assumptions and apply them in standard practice to make decisions. For a C/E threshold to work, decision-makers need a) to be delivering healthcare at maximum efficiency such that every healthcare input is deriving maximum health; b) have 'perfect information' so that decision-makers know the trade-offs in incremental cost per QALY of every existing intervention as well as the new intervention being evaluated.^{6,7} Both of these have to be satisfied to use C/E thresholds which should be addressed in ICER's 2020 value framework.
- **Threshold levels should adjust for inflation.** The USD \$50,000 cost per QALY threshold is widely believed to stem from Medicare coverage for patients with end-stage renal disease (ESRD) in the 1970s.⁸ Thresholds at a minimum should be adjusted for inflation, regardless of how they have been derived.^{9,10} By that accounting alone, a

\$50,000 threshold in 1972 adjusted for inflation would be equivalent to \$307,000 today, more than \$150,000 more than ICER's maximum threshold.¹¹

- **The impact of a cure on a population differs dramatically from chronic treatment: this necessitates cure specific-thresholds.** Gilead would like to recognize ICER's very encouraging efforts to address this important issue with its Cures Initiative, acknowledging that there are exciting opportunities to adapt HTA to more comprehensively address specific challenges in evaluating cures. It is important to note that a strong value framework can balance incentivizing curative treatments through assessments that holistically and comprehensively capture society's value for a cure, which is of far greater consequence than the value of chronic disease treatments. Gilead advocates the need for a separate cure specific threshold that is of a magnitude to attract future innovation.¹² Cure-specific thresholds should consider the availability of treatments (many vs. none), disease severity (*e.g.*, stroke, paralysis), mortality rates (*e.g.*, metastatic cancer), public health benefits (*e.g.*, eradication of HIV, HCV, Ebola), and societal impact (*e.g.*, antibiotic resistance, Alzheimer's disease, issues impacting children or caregivers). Without this consideration, C/E thresholds are intensely problematic as they have the potential to result in cures being devalued in comparison to chronic therapies.

2) USE OF BOTH THE QALY QUALITY ADJUSTED LIFE YEAR (QALY) AND THE EVLYG

ICER should considering enhancing the QALY and evLYG with additional methodologies to further characterize and measure the value a drug brings to the healthcare system.

- **ICER's addition of the evLYG adds further information and dimensionality for decision-makers above the QALY but there is the opportunity to enhance the existing value-framework to more specifically capture other elements of value.** Gilead recognizes ICER's work in adding the evLYG to provide further information on how life extension can be compared across treatments specifically where quality of life gains are limited. This is an important step towards driving greater inclusivity and equality within health technology assessment.
- **The underlying assumptions supporting the QALY have never been well validated, resulting in inconsistent outcomes from disease to disease.** A common assumption on the QALY is that it is an interchangeable unit of health status that can be applied across all diseases and it further represents the utility that society places on a given health state or outcome. Several studies demonstrate that health status and QALYs do not necessary correlate.^{13,14,15} In addition, the derivation of the QALY from quality of life measures (often performed in clinical trials) have significant variation and cannot be stated as equivalent to societal utility.^{16,17,18,19}

- **QALYs are an inaccurate measure of both health and societal value for treatment and health interventions.** QALYs inadequately address the heterogeneity of outcomes for available drug options across different diseases. They are difficult or impossible to accurately derive in the very young, elderly patient populations and other vulnerable individuals that are unable to advocate for themselves. QALYs also favor drugs for populations with mild disease compared to patients with lower baseline QALYs. The utility values that form the basis of a QALY calculation differ according to a) the method they are collected; b) from individual to individual; and c) when the same individual is asked the same questions to derive QALYs across different time periods. Also, QALYs do not account for impact on caregivers (spouses/family) and dependents (many who are children).^{20,21}
- **Discounting of benefits such as the QALY prioritizes the needs and health of current generations over those in the future.** Current methodologies for the estimation of value-based price not only discount costs but also discount outcomes such as the QALY or evLYG. Survival and benefit time horizons differ greatly between different diseases, and are especially long in the case of cures. Hence, the application of a constant discount rate can make the effect of benefits in the future fall close to zero.²² In essence, the benefits that a treatment brings that occur further in the future count for far less than outcomes today. In addition, discounting of benefits can also lead to double-counting such that an outcome measure may already reflect societal preferences for discounting (for example the time-trade-off derivation of the QALY);²³ and the further application of a discount rate amounts to discounting a benefit twice which has a large effect on reducing the calculated value of a drug.

3) METHODS TO INTEGRATE POTENTIAL BENEFITS, CONTEXTUAL CONSIDERATIONS, AND OTHER FACTORS RELEVANT TO JUDGMENTS OF AN INTERVENTION'S VALUE

ICER's value frameworks should continue work in more comprehensive assessment of benefits, contextual criteria and other factors that extend beyond currently applied measures therapeutic value.

- **The shortcomings of the QALY signal the need for additional methodologies to capture the value drugs create for patients and healthcare systems.** Most methodologies in the assessment of the value of new drugs have not changed materially for 30 years. Garber and Phelps (1997) provided microeconomic foundations for the incremental cost-effectiveness ratio based on QALYs, but experts agree an expansion of these foundations is needed.²⁴ Recent work in the economic evaluation of new technologies points to several elements of value that need further exploration and consideration within health technology assessment. These include work productivity, adherence-improving factors, reduced uncertainty (*e.g.*, through screening/diagnostics), reduced fear and risk of contagion, insurance value (*i.e.*, in this context defined as the availability of a treatment option if an individual gets a disease versus diseases that have

no treatment), severity of disease, value of hope, real option value, equity, and scientific spillovers and achievement of public health goals (e.g., reducing a transplant list, reduced transmission, disease elimination).²⁵ One option for addressing these factors is the use of multicriteria decision analysis (MCDA) which can include these factors.^{26,27,28} Another option is augmented cost-effectiveness analysis (ACEA).²⁹ Building on a traditional cost-effectiveness analysis, this allows stakeholders to evaluate policy with enhanced inclusion of value, areas such as prevention of financial risk, impact on private expenditure and distributional consequences across wealth strata and deaths averted. This has been used successfully in cures, for example, in tuberculosis to evaluate less traditional benefits such as prevention of secondary cases; and for funding of a vaccine to prevent rotavirus in Ethiopia and India.^{30,31} These are just two examples of value assessment innovations that could enhance ICER current value framework, demonstrating the possibilities for innovation in U.S. health technology assessment.

- ICER’s approach to assessing curative therapies will require significant innovation in order to capture their substantial value.** We welcome ICER’s Valuing a Cure Initiative and recommend that ICER consider modifying its value framework to account for broad areas of value derived from cures which are currently not captured. These important elements of societal benefit (mentioned in the paragraph above), while harder to measure, are reflective of society’s preference in measuring value, and are of great importance as they relate to newer innovative treatments and especially cures.³²
- Costs such those incurred by caregivers, patients and employers and outcomes such as increased ability to function and work are key concerns for ICER’s stakeholders, and should be reflected in the value framework base-case analyses.** The inclusion of costs not only incurred by the healthcare payer but also those incurred by the patient, employer and caregiver, including offsets in earnings, are fundamental to good health technology assessment practice (reflected in the global First (1996) and Second (2017) Panels on Cost-effectiveness).^{33,34} Excluding societal costs obscures cost savings and may result in the prioritization of inferior, less expensive therapies or chronic treatments over groundbreaking treatments. For example, in HIV/AIDS, before treatment and prevention such as PrEP, non-medical costs incurred by society were as much as 6.5 times direct medical costs.³⁵ Similarly, 80% of total costs for cirrhosis and chronic liver disease are indirect costs.³⁶ These costs must be reflected in value-based pricing to ensure the full value is captured. Another area is long-term care costs, which are an important consideration especially for Medicare beneficiaries, yet these costs are not included in the base-cases of the current value framework. Costs outside of those incurred by the insurance or a national payer should be inclusive of all stakeholders to address the magnitude of value for new treatments, which can be multiplicative especially for breakthrough treatments that cure or eradicate disease. Addressing factors such as patients going back to work, the benefit on caregivers, and the benefits to broader stakeholders (e.g., benefits to Medicare beyond the drug benefit, hospitalizations, but also home care, care givers and other benefits) may involve significant workload on ICER, but are critical for assessing the value of a treatment.

- **Value frameworks should incorporate appropriate assessment methodologies to account for new treatments impacting diseases where there are no alternatives.** New treatments introduced into care continuums where there have historically been no drug options, little or no cost and a weaker epidemiological understanding are disproportionately penalized in value framework assessments. Applying traditional willingness-to-pay thresholds has the potential to lead to the prioritization, acceleration and more comprehensive drug access in diseases with established treatments compared to diseases with no established treatments.
- **A more robust approach to time horizons is required to allow for more informed policy decisions.** Both short and longer term time horizons should be included in value frameworks, and value framework assessments should mirror the time horizon in the relevant pivotal clinical trial to reduce uncertainty and wait for real-world evidence (RWE) to reassess a product over longer time periods.
- **ICER should work to accommodate assessments of treatments approved with single-arm trials.** More and more breakthrough treatments especially in rare disease and oncology are approved on the basis of single-armed trials. This is increasingly important with the development and approval of more innovative therapies for vulnerable populations, including the CAR-T cancer therapies. Each situation in which a new drug is assessed in this context presents unique challenges. These can include sparse comparator data, a trial design that does not match how a product would be used in clinical practice, off label comparators, eligible patient populations different from trial populations. But most commonly problematic are comparisons to other trials with striking differences in patient population such that variation in effects cannot be compared in practice. ICER's value framework should ensure flexibility to address the variation in patient population, identification of the most relevant patient population and likely treatment use in clinical practice and heterogeneity of treatment effect.

In summary, Gilead appreciates the opportunity to provide comments on ICER's updated 2020 value framework and look forward to furthering the discussion on how to improve HTA methodology in the US. We believe ICER has the opportunity to advance practice on value assessment through considerations of the issues raised here about cost-effectiveness thresholds, QALYs, and contextual considerations.

Sincerely,



Bill Guyer
Senior Vice President and Head of Medical Affairs

REFERENCES

- ¹ Cameron D, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Global health action*. 2018 Jan 1;11(1):1447828.
- ² Vallejo-Torres L, García-Lorenzo B, Castilla I, Valcárcel-Nazco C, García-Pérez L, Linertová R, Polentinos-Castro E, Serrano-Aguilar P. On the estimation of the cost-effectiveness threshold: why, what, how?. *Value in Health*. 2016 Jul 1;19(5):558-66. [LINK](#)
- ³ Robinson LA, Hammitt JK, Chang AY, Resch S. Understanding and improving the one and three times GDP per capita cost-effectiveness thresholds. *Health Policy and Planning*. 2016 Jul 24;czw096. [LINK](#)
- ⁴ Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. *Bulletin of the World Health Organization*. 2015 Feb;93(2):118-24. [LINK](#)
- ⁵ Claxton, K., Sculpher, M., Carroll, S. Value-based pricing for pharmaceuticals: Its role, specification and prospects in a newly devolved NHS. *CHE Research Paper 60*. Feb 2011.
- ⁶ Mason J, Drummond M, Torrance G. Some guidelines on the use of cost effectiveness league tables. *Bmj*. 1993 Feb 27;306(6877):570-2. [LINK](#)
- ⁷ Briggs A, Gray A. Using cost effectiveness information. *Bmj*. 2000 Jan 22;320(7229):246. [LINK](#)
- ⁸ Grosse SD. Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY threshold. Expert review of pharmacoeconomics & outcomes research. 2008 Apr 1;8(2):165-78. [LINK](#).
- ⁹ Grosse SD. Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY threshold. Expert review of pharmacoeconomics & outcomes research. 2008 Apr 1;8(2):165-78. [LINK](#).
- ¹⁰ Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the \$50,000-per-QALY threshold. *New England Journal of Medicine*. 2014 Aug 28;371(9):796-7. [LINK](#).
- ¹¹ Bureau of Labor and Statistics. CPI inflation calculator. April 1972- April 2019. [LINK](#).
- ¹² Garrison LP. Rewarding value creation to promote innovation in oncology: The importance of considering the global product life cycle. *Oncologist*, 2009 July 15 (Supplement 1), 49-57. [LINK](#)
- ¹³ Usman A, Lewis S, Hinsliff-Smith K, Long A, Housley G, Jordan J, Gage H, Denning T, Gladman JR, Gordon AL. Measuring health-related quality of life of care home residents: comparison of self-report with staff proxy responses. *Age and ageing*. 2019 Jan 7:1-7. [LINK](#)
- ¹⁴ Kularatna S, Byrnes J, Chan YK, Ski CF, Carrington M, Thompson D, Stewart S, Scuffham PA. Comparison of the EQ-5D-3L and the SF-6D (SF-12) contemporaneous utility scores in patients with cardiovascular disease. *Quality of Life Research*. 2017 Dec 1;26(12):3399-408.
- ¹⁵ Lorgelly PK, Doble B, Rowen D, Brazier J. Condition-specific or generic preference-based measures in oncology? A comparison of the EORTC-8D and the EQ-5D-3L. *Quality of Life Research*. 2017 May 1;26(5):1163-76. [LINK](#)
- ¹⁶ Sopina E, Chenoweth L, Luckett T, Agar M, Luscombe GM, Davidson PM, Pond CD, Phillips J, Goodall S. Health-related quality of life in people with advanced dementia: a comparison of EQ-5D-5L and QUALID instruments. *Quality of Life Research*. 2019 Jan 15;28(1):121-9. [LINK](#)
- ¹⁷ Ombler F, Albert M, Hansen P. How Significant Are “High” Correlations Between EQ-5D Value Sets?. *Medical Decision Making*. 2018 Aug;38(6):635-45.
- ¹⁸ Wijnen BF, Mosweu I, Majoie MH, Ridsdale L, de Kinderen RJ, Evers SM, McCrone P. A comparison of the responsiveness of EQ-5D-5L and the QOLIE-31P and mapping of QOLIE-31P to EQ-5D-5L in epilepsy. *The European Journal of Health Economics*. 2018 Jul 1;19(6):861-70. [LINK](#)
- ¹⁹ Kularatna S, Byrnes J, Chan YK, Carrington MJ, Stewart S, Scuffham PA. Comparison of contemporaneous responses for EQ-5D-3L and Minnesota Living with Heart Failure; a case for disease specific multiattribute utility instrument in cardiovascular conditions. *International journal of cardiology*. 2017 Jan 15;227:172-6.

-
- ²⁰ Pettitt DA, Raza S, Naughton B, Roscoe A, Ramakrishnan A, Ali A, Davies B, Dopson S, Hollander G, Smith JA, Brindley DA. The limitations of QALY: a literature review. *Journal of Stem Cell Research and Therapy*. 2016 Jan 1;6(4). [LINK](#)
- ²¹ Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. Oxford university press; 2015 Sep 25.
- ²² Attema AE, Brouwer WB, Claxton K. Discounting in economic evaluations. *PharmacoEconomics*. 2018 May 19;1-4. [LINK](#)
- ²³ *Op. Cit.* Attema *et al.* [LINK](#)
- ²⁴ Garber AM, Phelps CE. Economic foundations of cost-effectiveness analysis. *Journal of health economics*. 1997 Feb 1;16(1):1-31.
- ²⁵ Lakdawalla DN, Doshi JA, Garrison Jr LP, Phelps CE, Basu A, Danzon PM. Defining elements of value in health care—a health economics approach: an ISPOR Special Task Force report [3]. *Value in Health*. 2018 Feb 1;21(2):131-9.
- ²⁶ Phelps CE, Lakdawalla DN, Basu A, Drummond MF, Towse A, Danzon PM. Approaches to aggregation and decision making—a health economics approach: an ISPOR Special Task Force report [5]. *Value in Health*. 2018 Feb 1;21(2):146-54.
- ²⁷ Adunlin G, Diaby V. Application of multicriteria decision analysis in health care: a systematic review and bibliometric analysis. *Health Expectations*. 2015 Dec; 18(6): 1894-905. [LINK](#)
- ²⁸ Thokala P, Duena A. Multiple criteria decision analysis for health technology assessment. *Value Health*. 2012 Dec; 15(8): 1172-81. [LINK](#)
- ²⁹ Phelps CE, Lakdawalla DN, Basu A, Drummond MF, Towse A, Danzon PM. Approaches to aggregation and decision making—a health economics approach: an ISPOR Special Task Force report [5]. *Value in Health*. 2018 Feb 1;21(2):146-54.
- ³⁰ Verguet S, Laxminarayan R, Jamison DT. Universal public finance of tuberculosis treatment in India: an extended cost-effectiveness analysis. *Health economics*. 2015 Mar;24(3):318-32. [LINK](#)
- ³¹ Verguet S, Murphy S, Anderson B, Johansson KA, Glass R, Rheingans R. Public finance of rotavirus vaccination in India and Ethiopia: an extended cost-effectiveness analysis. *Vaccine*. 2013 Oct 1;31(42):4902-10. [LINK](#)
- ³² Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care – Health Economics Approach: An ISPOR Special Task Force Report. *Value in Health*. 2018 Feb; 21(2):131-139. [LINK](#)
- ³³ Weinstein, MC *et al.* Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *Jama*. 1996 Oct 16;276(15):1253-8. [LINK](#)
- ³⁴ *Cost-Effectiveness in Health and Medicine*. Ed. Newmann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Oxford University Press, New York 2017.
- ³⁵ Scitovsky AA, Rice DP. Estimates of the direct and indirect costs of acquired immunodeficiency syndrome in the United States, 1985, 1986, and 1991. *Public Health Reports*. 1987 Jan;102(1):5.
- ³⁶ Ruhl CE *et al.* Costs of digestive diseases. In: Everhart J, editor. *The Burden of Digestive Diseases in the United States*. Washington, DC: NIH publication; 2008. pp. 137–143. US Dept of Health and Human Services, Public Health Service, National Institutes of Health, and National Institute of Diabetes and Digestive and Kidney Diseases. 09-6443.

June 7, 2019

Steven D. Pearson, MD, MSc
Institute for Clinical and Economic Review
Two Liberty Square, 9th floor
Boston, MA 02109

Martin D. Marciniak, Ph.D.
Vice President
US Medical Affairs,
Customer Engagement,
Value Evidence & Outcomes
GlaxoSmithKline

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398
Tel. 919-483-1959
www.ask.com

Re: GSK Recommendations for the 2019 Update of ICER's Value Assessment Framework

Dear Dr. Pearson:

GSK appreciates the opportunity to provide recommendations for the 2019 Update of the ICER Value Assessment Framework (VAF). As an innovation leader, GSK envisions — *a sustainable, evidence-based US healthcare ecosystem* — that ensures improved patient outcomes and rewards innovation. We believe that value in healthcare should encompass the holistic benefits and costs as experienced by patients and society, over time. To this end, GSK is committed to engaging with US value assessment organizations and supporting the advancement of transparent methods to aid decision-making in healthcare. As shared in our previous comment letters to ICER, GSK recommends the development and application of dynamic VAFs that incorporate adhere to the following principles:

- 1) Are patient-centered and fully account for patient priorities and preferences, and where appropriate, caregiver perspectives,
- 2) Quantify healthcare value with transparency and methodological rigor,
- 3) Accurately capture the complexities of diseases and clinical pathways as evidence matures,
- 4) Tangibly connect access and reimbursement to healthcare value,
- 5) Support health policy decision-making that fosters innovation.

For ease of review, we have categorized our 2019 recommendations into five core topics: (A) Enhancing the ICER Value Assessment Process, (B) Prioritizing Patients' and Care-givers' Voices and Evidence in Value Assessments, (C) Willingness to Pay Thresholds, (D) Quantifying the Magnitude and Certainty of Innovative Therapies, and (E) Alternative Approaches to Quantifying the Value.

(A) Enhancing the ICER Value Assessment Process

ICER should be commended for their commitment to continuous improvement (e.g., iterative updates to ICER's VAF, economic model pilot, and academic data in confidence policy). It is important these processes continue and/or expand. In the majority of assessments conducted since the 2017 update of ICER's VAF, US healthcare stakeholders have called upon ICER to enhance stakeholder engagement, increase the adequacy and consistency of evidence, and improve transparency in ICER's methods and processes.¹ These important issues will continue to challenge ICER's credibility amongst patients, providers, manufacturers, and academic experts.

¹ A. Kanaskar, et al. Evaluation of the Institute for Clinical and Economic Review (ICER) Public Engagement Process: Stakeholder Comment Analysis. PNS173. ISPOR 2019 New Orleans, LA

GSK believes that on-going transparency and engagement challenges within the ICER value assessment process may be ameliorated by more standardization and broader disclosure, as exemplified by the Advisory Committee on Immunization Practices (ACIP).² ACIP's Evidence to Recommendations Framework is the gold-standard by which US vaccine policy recommendations are developed, harmonized, and re-evaluated in alignment with innovation and public health priorities.

The key domains of ACIP structure and process— objectivity, credibility, utility, transparency, and timeliness of updates — which have made it foundational to the development of national vaccine policy, may be equally valuable to ICER. As summarized in Table 1, there are key differences between ACIP and ICER in terms of appraisal committee membership and structure, disclosure of conflicts of interest policy, structure of research work groups, and the number of multi-stakeholder meetings for a given value assessment. These differences reflect opportunities for ICER to address its transparency and engagement challenges.

Recommendation: *We urge ICER to adopt the following recommendations into its VA process:*

1. *Restructuring of Appraisal Committees, Including Expanded Representation of Patient Groups and Disability Advocates as Voting Members*
 - a. *GSK recommends that ICER reconsider the current appraisal committees' membership process. Expanded inclusion of disease specific patient groups, disability advocates, clinical and economic academic experts are recommended to complement payer perspectives.*
 - b. *GSK recommends that ICER foster depth of expertise and consistency across appraisal committees by assigning permanent topic areas to existing and future appraisal committees.*
2. *Managing Potential Conflicts of Interest*
 - a. *GSK recommends that ICER publicly disseminate the policy on conflicts of interest for appraisal committee members.*
 - b. *GSK recommends that ICER includes in its conflicts of interest policy for appraisal committee members which require an annual public disclose of conflicts of interests.*
3. *Establishment of Value Assessment Research Workgroups, including Patient Representatives*
 - a. *GSK recommends that ICER establish research workgroups for topic/therapeutic areas and expand workgroup memberships to patient representatives as well as other lay and academic stakeholders.*
 - b. *GSK recommends that ICER foster expertise and consistency by assigning permanent topic/therapeutic areas to its US academic collaborators.*
4. *Broadening Patient Engagement and Trust in the ICER VA Process*
 - a. *GSK recommends that ICER adopt ACIP multi-public meeting approach, providing 2-3 additional opportunities for the patient groups and other stakeholders to provide comments to an initial draft report and an updated draft report, prior to final appraisal committee voting.*
 - b. *GSK recommends that ICER disclose explicit contributions of ICER staff to a given value assessment, including authorship contributions to the final reports and policy recommendations.*
 - c. *GSK recommends that ICER adopt the ACIP approach and employ external clinical and economic experts to validate all draft and final reports as well as make public, executable model files.*

² <https://www.cdc.gov/vaccines/acip/recs/index.html>

- d. *GSK recommends that ICER establish a standard process to remove or redact reports from ICER website, when errors have been reported by stakeholders.*

(B) Prioritizing Patients' and Care-givers' Voices and Evidence in Value Assessments

GSK is committed to championing for the meaningful inclusion of patients and care-giver perspectives and evidence in value assessments. Our position is aligned to the key recommendations on delivery of quality, patient-centered care^{3,4} and the National Health Council's Patient-Centered Value Model Rubric (The Rubric)⁵. It is also supported by a growing body of research, which shows that patients' perceptions of healthcare value are highly heterogeneous, varying significantly between symptom severity and disease course across indications, and even within the same disease.^{6,7} For example, a metastatic cancer patient may set a higher value for a treatment that delivers comparable overall survival but less fatigue so that they may return to work.^{7,8} Similarly, a lupus patient may value a therapy that reduces lupus flares, over and above standard of care alone, if their flare symptoms manifest as a facial "butterfly rash" which may stigmatize them and hinder their ability to socially or occupationally function.

Healthcare value also extends beyond the patient, as caregivers of seriously ill patients experience significant financial and psycho-social burden.^{9,10,11} Family spillover benefits, i.e., improvements in patients' health and outcomes resulting from new innovative therapies, may substantially offset unpaid care-giving or potentially provide quality of life gains attributed to the caregiver.^{12,13} Thus we contend that any quantification of healthcare value, in the absence of patient and care-giver perspectives and evidence on the most important benefits, risks, and trade-offs, is fundamentally incomplete.

Recommendation: *GSK is encouraged by ICER's commitment to "encompass and reflect the experiences and values of patients". In addition to our explicit recommendations above to broaden patient engagement and representation in ICER's value assessment process, we recommend that ICER expand the inclusion of quantitative and qualitative patient and care-giver evidence, including patient -reported outcomes, psycho-social burden, and preferences data into its value assessments.*

³ Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: National Academies Press, 2001.

⁴ Beal A, Sheridan S. Understanding the patient and family engagement rubric. Available from: <http://www.pcori.org/assets/2014/06/PCORI-AcademyHealth-ARM-Beal-060914.pdf>. [Accessed October 9, 2016].

⁵ Patient-Centered Value Model Rubric Released "National Health Council Shares Guidance for Assessing the Value of New Treatments. <http://www.nationalhealthcouncil.org/patient-centered-value-model-rubric-released>. Accessed 16 March, 2017.

⁶ Fowler FJ Jr, Levin CA, Sepucha KR. Informing and involving patients to improve the quality of medical decisions. *Health Affairs (Millwood)*, 2011; 30: 699–706

⁷ Food and Drug Administration. Voice of the patient: lung cancer. Available from: <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM379698.pdf>.

⁸ Tevaarwerk AJ, Lee JW, Terhaar A, et al. Working after a metastatic cancer diagnosis: factors affecting employment in the metastatic setting from ECOG-ACRIN's Symptom Outcomes and Practice Patterns study. *Cancer*. 2015;122(3):438-446.

⁹ Bevans, Margaret F., and Esther M. Sternberg. "Caregiving Burden, Stress, and Health Effects Among Family Caregivers of Adult Cancer Patients." *Jama* 307.4 (2012): 398–403.

¹⁰ Milbury, K., et al., Longitudinal associations between caregiver burden and patient and spouse distress in couples coping with lung cancer. *Supportive Care in Cancer*, 2013. 21(9): p. 2371-2379.

¹¹ Buchanan, R.J., D. Radin, and C. Huang, Caregiver burden among informal caregivers assisting people with multiple sclerosis. *International journal of MS care*, 2011. 13(2): p. 76-83.

¹² Brouwer WBF. The Inclusion of Spillover Effects in Economic Evaluations: Not an Optional Extra. *Pharmacoeconomics*. 2018;37:451–6.

¹³ Prosser, L., Wittenberg, E. Advances in Methods and Novel Applications for Measuring Family Spillover Effects of Illness. *Pharmacoeconomics*. April 2019, Volume 37, Issue 4, pp 447–450

(C) Willingness to Pay Thresholds

GSK supports robust dialogue on the evolving definitions and thresholds for value. To date, we have limited insight on US societal willingness to pay (WTP) for healthcare or origins for commonly cited WTP thresholds.¹⁴ The current body of evidence to support a US societal perspective on willingness to pay for common disease treatments is thin, especially in the context of durable and potentially curative therapies. Of the few studies that have been published, WTP among US stakeholders is highly variable, patient specific and disease dependent.^{15,16,17} Moreover, evidence suggests that the different approaches to value assessment may result in conflicting conclusions, thereby hindering health policy decision making.¹⁸ The totality of these considerations question the rationale of a singular value-based price or WTP threshold. At a minimum, a more expansive definition of the WTP corridor for therapies by potential health benefit is necessary.

Recommendation: *We recommend that ICER explore the utility of situationally specific thresholds for therapies that treat common diseases, oncology/rare diseases, and curative one-time therapies. Identification and validation of specific WTP thresholds should be established as part of multi-stakeholder research studies, using approaches such as conjoint analyses and mixed methods to quantitatively and qualitatively assess US societal preferences.*

(D) Quantifying the Magnitude and Certainty of Net Health Benefit for Innovative Therapies

With the emergence of innovative healthcare technologies such as cell and gene therapies, we are entering an unprecedented era of durable and potentially curative treatments for patients and society. Never has it been more critical to ensure that US VAFs are fit for purpose, namely — to objectively and transparently quantify the value of a health technology to society in the presence of evidence uncertainty. Thus, we question the utility of the ICER's Evidence Rating Matrix (ERM) to adequately assess the quality and certainty of clinical evidence for such innovative therapies. The ERM's level of certainty is based on a “conceptual confidence interval” of existing evidence.¹⁹ The five domains of the EBM that are used to anchor the “conceptual confidence interval” (Level of Bias, Applicability, Consistency, Directness, and Precision) handicaps any indications wherein evidence generation is challenged by the inherent uniqueness of the disease. For example, orphan diseases, in which evidence generation is challenging because of small patient populations, misdiagnoses and poor surveillance as well as discontinuous access to specialty care centers, are at high risk of being systematically disadvantaged by the use of the EBM in value assessments.^{8,20}

Recommendation: *We recommend that ICER discontinue the use of its ERM for assessment of orphan diseases and indications with small patient populations, to account for the challenges of evidence generation in these patient groups. We recommend that ICER explore other means to quantify the potential impact that additional evidence would have on the ICER's value assessments, such as value of information analyses.*

¹⁴ Neumann, P. J., Cohen, J. T., & Weinstein, M. C. (2014). Updating Cost-Effectiveness—The Curious Resilience of the \$50,000-per-QALY Threshold. *N Engl J Med*, 371(9), 796-797. doi:10.1056/NEJMp1405158

¹⁵ Braithwaite, R.S., et al., What does the value of modern medicine say about the \$50,000 per quality-adjusted life-year decision rule? *Medical care*, 2008. 46(4): p. 349-356.

¹⁶ Hirth, R.A., et al., Willingness to pay for a quality-adjusted life year in search of a standard. *Medical Decision Making*, 2000. 20(3): p. 332-342.

¹⁷ Seabury, S.A., et al., Patients value metastatic cancer therapy more highly than is typically shown through traditional estimates. *Health Affairs*, 2012. 31(4): p. 691-699.

¹⁸ Buchanan J, Wordsworth S. Welfarism versus extra-welfarism: can the choice of economic evaluation approach impact on the adoption decisions recommended by economic evaluation studies? *PharmacoEconomics*. 2015;33(6):571–9.

¹⁹ ICER Evidence Rating Matrix. <http://icer-review.org/wp-content/uploads/2016/02/Rating-Matrix-User-Guide-UPDATED-06.30.17.pdf>

²⁰ ICER Orphan Drug Assessment: Final Framework Adaptations. <https://icer-review.org/material/final-ultra-rare-adaptations/>

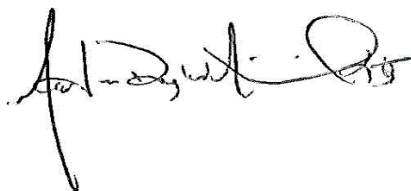
(E) Alternative Approaches to Quantifying the Value

The shortcomings of current US value assessment frameworks to fully capture all the elements that are relevant to a treatment's value has been highlighted by International Society for Pharmacoeconomic and Outcomes Research's Special Task Force on U.S. Value Assessment Frameworks.²¹ Value elements such as the value of knowing, real option value, value of hope, insurance value, and scientific spillovers are relevant to patients and society.^{22, 23} GSK supports the expansion and evolution of VAFs that incorporate a wider range of the elements of value, beyond the direct and indirect costs as well as net benefit which are a part of standard cost-effectiveness methods.

Recommendation: *GSK recommends ICER re-explore value assessments using alternative approaches such as multi-criteria decision-analysis (MCDA)^{24,25} and more novel approaches such as the Burden Augmented by Deadliness and Impact (BADI)²⁶, which may more efficiently capture aspects of value to health and non-health society benefits such as equity and social determinants of health.*

GSK appreciates the opportunity to share our recommendations with ICER. We look forward to exploring these and other related issues in greater depth in the future with you. Please feel free to contact us should you wish to discuss these recommendations in further detail.

Sincerely,



Martin D. Marciniak, Ph.D.

Vice President

US Medical Affairs, Customer Engagement,
Value Evidence and Outcomes

²¹ Garrison LP, Neumann PJ, Willke RJ. A health economics approach to US value assessment frameworks—summary and recommendations of the ISPOR special task force report [7]. *Value in Health* 2018;21(2):161–5.

²² L. Garrison, J. Mestre-Ferrandiz, B. Zamora. *The Value of Knowing and Knowing the Value: Improving the Health Technology Assessment of Complementary Diagnostics*, Office of Health Economics and EPEMED, Luxembourg, Luxembourg (2016);

²³ L.P. Garrison, S. Kamal-Bahl, A. Towse. Toward a broader concept of value: identifying and defining elements for an expanded cost-effectiveness analysis. *Value in Health*, 20 (2) (2017), pp. 213-216

²⁴ C. Phelps, M. Guruprasad, Using Multicriteria Approaches to Assess the Value of Healthcare, *Value in Health* 2017; 20:151-155

²⁵ Jit M. MCDA from a health economics perspective: opportunities and pitfalls of extending economic evaluation to incorporate broader outcomes. *Cost Effectiveness and Resource Allocation*. 2018 Nov;16(1):45.

²⁶ Caro J. Novel Approaches to Value Assessment, Beyond Cost-Effectiveness Framework. 2018. https://www.ispor.org/docs/default-source/presentations/1245_beyond_cea_caro.pdf?sfvrsn=6bf69213_0

Table 1. Comparison of ACIP vs ICER Structure and Processes

Domains	ACIP	ICER	GSK Recommendations
1. Funding sources	CDC /DHHS 2019 operating cost: \$130, 963 Staff costs: \$343,823	77% - Other Non-profit organizations, including Arnold Foundation's \$13.9M 3-year grant (2017- 2020)	N/A
2. Governance	ACIP report to CDC Director, who reports to Secretary of DHHS	ICER president and executive team are guided by a governance board and advisory board	
3. Appraisal Committee Structure	<ul style="list-style-type: none"> 15 total voting members: 1 chair, 1 consumer representative, 13 experts in specific disciplines 8 ex-officio members of federal agencies 26 non-voting members of liaison organizations Applications for ACIP membership reviewed by Secretary of DHHS 	3 separate appraisal committees: <ul style="list-style-type: none"> CTAF, Midwest CEPAC, New England CEPAC <ul style="list-style-type: none"> ➤ Majority of committee members are payers or PBMs, IDN executives ➤ Membership is by application and review process is unclear. 	<ul style="list-style-type: none"> ▪ <i>Recommend that ICER reconsider the appraisal committees' membership. Expanded inclusion of clinical and economic academic experts are recommended to complement the payer perspectives.</i> ▪ <i>Recommend that ICER foster depth of expertise and consistency across appraisal committees voting by assigning permanent topic areas to existing appraisal committees.</i>
4. Management of Conflicts of Interest	<ul style="list-style-type: none"> People with specific vaccine-related interests are not considered for appointment. ACIP members are required to file confidential financial reports annually with the Office of Government Ethics and to disclose publicly all vaccine related interests and work, including participation in clinical trials, at each meeting. 	<ul style="list-style-type: none"> It is unclear how ICER reviews and manages conflicts of interest for appraisal committee members. 	<ul style="list-style-type: none"> ▪ <i>Recommend that ICER revise policy on conflicts of interest for appraisal committee members to require annual public disclosure of conflicts of interests,</i> ▪ <i>Recommend that ICER publicly disseminate the appraisal committee policy on conflicts of interest for members</i>
5. Research Workgroups	<ul style="list-style-type: none"> ACIP workgroups, both permanent and topic focused, are formed as a resource for synthesis and analysis of evidence for ACIP review and deliberation. All workgroups are chaired by an ACIP member, includes at least 2 ACIP members and a CDC subject-matter expert. Vaccine manufacturers cannot serve on the workgroups; but provide testimony as solicited. 	<ul style="list-style-type: none"> ICER has established a network of US academic collaborators to conduct core elements of the value assessment, including systematic evidence review, comparative effectiveness analyses, and economic modelling. ICER also conducts its own value assessments, using its research team. It is unclear the involvement of ICER staff on specific value assessments, however all final reports are attributed to ICER leadership. 	<ul style="list-style-type: none"> ▪ <i>Recommend that ICER broaden research workgroups participation to members of the public</i> ▪ <i>Recommend that ICER foster expertise and consistency by assigning permanent topic areas to its US academic collaborators</i>
6. Process	<ul style="list-style-type: none"> ACIP meeting topics are solicited from CDC subject-matter experts; ACIP members, ex officio members and liaisons; academic consultants; and ACIP workgroup members. All workgroup findings and options are presented to the ACIP in three 	<ul style="list-style-type: none"> ICER topics are selected by ICER leadership and staff, based on horizon scanning and solicitation of members. Topics are announced in Q4 of the preceding year. It is unclear on how topics are assigned to specific appraisal 	<ul style="list-style-type: none"> ▪ <i>Recommend that ICER disclose explicit contributions of ICER staff to a given value assessment report.</i> ▪ <i>Recommend that ICER adopt ACIP multi-public meeting approach, providing 2-3</i>

Domains	ACIP	ICER	GSK Recommendations
	<p>regularly scheduled public meeting annually.</p> <ul style="list-style-type: none"> Meeting dates are posted 4 years in advance. Workgroup evidence summary and draft recommendations are deliberated until ACIP members reach a majority decision. Public comments also are solicited during each ACIP meeting and are considered in the decision-making process. These inputs are synthesized by the workgroup in an iterative process, and options are re-presented to the ACIP for final consideration and vote. 	<p>committees and/or academic collaborators</p> <ul style="list-style-type: none"> ICER value assessment process is approximately 32 weeks, including <ul style="list-style-type: none"> Topic selection Draft & Final Scope Protocol Review Draft Evidence Report Pre-Public Meeting Evidence Report Public Meeting Final Report. ICER reports that it has 6 touches - points with patient groups for a given topic review 	<p><i>additional opportunities for the public and patient groups to provide comments to an initial draft report and an updated draft report, prior to final appraisal committee voting.</i></p>
7. Clinical Evidence Thresholds	<ul style="list-style-type: none"> In 2010 ACIP adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for developing evidence-based recommendations. <ul style="list-style-type: none"> Category A: Recommendation that applies to all persons in an age- or risk-based group. Category B: Recommendation for individual clinical decision making. No recommendation/unresolved issue. 	<p>ICER uses a de novo evidence rating system, which attempts to associate the uncertainty in the body of evidence to the magnitude of comparative clinical benefit.</p> <ul style="list-style-type: none"> Rating range from substantial Net Benefit (A) to Negative Net Benefit; High to Low Evidence Certainty. 	<ul style="list-style-type: none"> <i>Recommend that re-anchor its rating scale such that A+ is the highest benefit rating.</i>
8. Economic Thresholds	<ul style="list-style-type: none"> The ACIP does not use a “cut-off” to determine whether a vaccine is cost-effective. Cost-effective only 1 factor considered in development of immunization recommendations. 	<p>ICER using a willingness to pay threshold, ranging from \$50K/QALY to \$150K/QALY</p> <p>BI Annual Threshold: \$991M</p>	<ul style="list-style-type: none"> <i>Recommend that ICER adopt ACIP approach, eliminating the range used for the value -based pricing benchmark entirely.</i>
9. Quality Control	<ul style="list-style-type: none"> All evidence is reviewed and deliberated by workgroup members prior to presentation to ACIP. Additionally, all economic analyses are reviewed by a CDC health economist or other qualified economist before presentation to the ACIP. 	<p>ICER engages external clinical experts for review of draft deliverables. However, recent experience with 2018 asthma review suggests that ICER may at times, lack access to appropriate experts (food allergist vs respiratory pulmonologist) or solicit review from individuals with providing sufficient time to review (AAFA).</p>	<ul style="list-style-type: none"> <i>Recommend that ICER adopt ACIP approach, to employ external clinical and economic experts to review draft and final reports as well as provide open, executable model files.</i> <i>ICER should establish a policy to remove draft or final reports from the public domain, if any errors have been reported by external stakeholders.</i>



June 10, 2019

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

Submitted Electronically: publiccomments@icer-review.org

RE: 2020 Update to ICER Value Framework

Dear Dr. Pearson,

Haystack Project appreciates the opportunity to respond to the Institute for Clinical and Economic Review's (ICER's) national call for suggestions on how to improve its value assessment framework.

Haystack Project is a non-profit organization enabling 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.

The Rare Cancer Policy Coalition (RCPC) is a Haystack Project initiative that brings together rare cancer patient organizations. RCPC gives participants a platform for focusing specifically on systemic reimbursement barriers and emerging landscape changes that impact new product development and treatment access for rare cancer patients. It is the only coalition developed specifically to focus attention on reimbursement, access and value issues across the rare cancer community. Working within the Haystack Project enables RCPC participants and rare and ultra-rare patient advocates to leverage synergies and common goals to optimize advocacy in disease states where unmet need is high and treatment inadequacies can be catastrophic.

We believe that one of the largest obstacles to effectively reducing health care costs while enhancing, or at least not compromising, care for individuals with rare diseases is the risk of unintended consequences to these populations. We have, therefore, outlined some of the challenges patients with rare and ultra-rare diseases and rare cancers face within the context of the ICER value framework and its reliance on population-level indices of quality and value.

BACKGROUND

Over 35 years ago, Congress recognized that commercial realities associated with research and development discouraged innovation in treating serious medical conditions affecting small populations. Countless lives have been improved, or saved, by new therapies stimulated by the set of statutory incentives for orphan drugs. Although millions of Americans affected by a rare disease are still waiting and hoping for treatment or a cure, there are many for whom treatments that are already available or in the pipeline are out of reach due to the realities of current reimbursement structures.

- 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.

Innovation in how we understand and address disease mechanisms are currently advancing at a previously unthinkable pace. Targeted cancer treatments, gene therapy and regenerative medicine, and immunologic approaches to rare, serious, and life-threatening conditions give renewed hope to patients and their caregivers. Novel treatments have, however, been accompanied by increased concerns that the treatments we need will unduly burden overall health care costs.

ICER's decision to devise 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 responded to ICER's call for comments with guarded optimism, while noting 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." Today, Haystack Project has significant concerns with ICER's assessments evaluating treatments for rare and ultra-rare conditions, including rare cancers, under the 2017-2019 framework, and the increased willingness and interest among payers to utilize these assessments.

While Congress' action on orphan drugs 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 for which there are no comparable treatment options, the 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. Unfortunately, we now face an innovation environment with high potential that on-label

competition will negate enhanced market exclusivity, and a payer landscape evolving toward enhanced scrutiny on manufacturer pricing decisions.

We have grave concerns that ICER's enthusiasm for early review of rare and ultra-rare disease and rare cancer treatments will tip the scales to discourage investment in research and discovery unless patient populations are sufficient to support short-term return on investment. While ICER's assessment of CAR-T cell therapy for B-cell acute lymphoblastic yielded a determination of "good cost-effectiveness," the review of CAR-T for adult cancer indications went beyond ICER's stated goal of a cost-effectiveness determination to include recommendations for coverage and use. The Medicare program, characterized ICER's work as a technology assessment, seized upon ICER "concerns" that the pivotal clinical trials were single-arm studies without the high number of participants over age 65 to justify specific geriatric labeling, and proposed a coverage mechanism (coverage with evidence development) reserved for unproven technologies. The resulting draft decision incorporated ICER "recommendations" that were not evidence-based (e.g., registry requirements in addition to those required by FDA). We urge ICER to recognize that studies of new rare cancer treatments directed toward patients with high short-term mortality and no remaining treatment options cannot ethically randomize patients to palliative care once potential efficacy is established. If ICER continues to characterize this reality as an evidence deficiency, many patients will be unable to access life-saving therapies targeted to their rare cancers.

ICER's discussion of CAR-T cost-effectiveness in its recent review of Spinraza and Zolgensma for Spinal Muscular Atrophy (SMA) yielded the dire statement that "[t]he US health care system cannot sustain paying prices far above traditional cost-effectiveness levels for the growing tide of treatments for ultra-rare disorders." SMA is a catastrophic disorder with some subtypes sufficiently severe to make it unlikely that a baby will survive to age two. ICER's New England CEPAC acknowledged "the remarkable effectiveness and many additional potential benefits and contextual considerations of Spinraza and Zolgensma" when it unanimously voted that Spinraza - until very recently, the only SMA treatment available - represented low long-term value for the money due to its high price. Spinraza was introduced to the market in 2016, but Zolgensma was not even commercially available at the time of ICER's review.

ICER has stated that "the goal of cost-effectiveness analysis is to help inform policy that will ensure truly transformative treatments are rewarded handsomely, while neither patients nor society pays too much for care that doesn't offer patients significant benefit."¹ While one would expect that a treatment demonstrating "remarkable effectiveness" would be viewed as offering patients significant benefit, ICER's selection of a model team for the SMA evaluation made it unlikely, if not impossible, that it would. The University of Sheffield group ICER relied upon had used its model to oppose UK patient access to Spinraza in early August 2018,² before ICER released its draft scoping document.

While ICER cited the CAR-T example in its SMA review to illustrate that it is "possible" for a high-cost treatment to demonstrate good cost-effectiveness in a life-threatening rare condition, it is far more likely that novel approaches to these conditions will not clear ICER's hurdles until they have been used in clinical practice for a sufficient number of years to establish that the

value demonstrated in FDA pivotal trials translates to ICER's view of value over the long-term. Even then, the treatments we need – existing and yet-to-be-developed – will not demonstrate “value” unless that concept is relevant to the disease and its small patient population, and the model reflects the values of the US health care system.

Foundational assumptions and policy goals driving ICER's framework

ICER has articulated its guiding principle of attempting to balance competing ethical interpretations of “fairness” in the context of health care spending on costly treatments. 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 Haystack Project participants include patients with serious rare and ultra-rare disorders and rare cancers, their caregivers, as well as those who have experienced the life-changing loss of a loved one to a disease for which no treatment exists. We remain concerned that Hughes’ world-view, if further operationalized and implemented to drive treatment and reimbursement decisions, paints a dark future for individuals with rare and 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 or rare cancer, simply by virtue of utilitarian principles.

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 health care coverage. The US health care system is not driven by vertical equity. In fact, it 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 rare with one, costly, available treatment.

Haystack Project and RCPC members support efforts to expand equitable access to quality health care. We are, however, concerned that ICER's efforts to date, particularly in addressing the unique challenges associated with rare and ultra-rare diseases and rare cancers 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) on early stage projects.⁵⁶

Haystack Project and RCPC Oppose ICER's Use of a One-Size-Fits-All Threshold Range and Assessment of “Budget Impact”

ICER's "one-size-fits-all" cost-per-QALY threshold is known to be inherently biased against the oldest and sickest patients, as well as those with the rarest diseases. Not only does it skew against patients with disabilities, but the ICER threshold has not been validated in the US or shown validity across each disease, patient group, and medical situation. We urge ICER to devise cost-per-QALY thresholds that are flexible and appropriate to the US health care system and the condition being treated. Special considerations such as upwardly skewed age distribution, excessive discounting of life years based on sicker patients or disability, orphan disease status, and potential horizon market entries likely to impact market share must be included in the analysis.

Haystack Project and RCPC are similarly concerned that ICER has conflated value and cost, and that its use of budget impact thresholds furthers that distortion toward arbitrariness. ICER's panel composition and payer-based perspective create inherent biases against high-cost treatment options. When budget impact is the central determinant of value, stakeholders do not have the benefit of a true assessment of value that acknowledges patients and their right to and expectation of coverage for medically necessary treatments.

ICER's call for comments included the statement that

[w]hen annual US spending on a specific drug is likely to exceed this threshold, ICER's report will highlight potential short-term affordability and access challenges. The report will also include the *maximum percentage of eligible patients* who would be able to receive the therapy, at multiple possible price points, without exceeding the threshold. (emphasis added)

We urge ICER to remove budget as a key driver in determining health system value, and reconsider its proposal to include what we, as patients and caregivers, view as a false decision mandate, i.e., outlining a set of price points and associated percentages of patients that would receive or be denied treatment. The US health care system is centered on the proposition that quality care is an investment, not a consumption. ICER's assessments should reflect this foundational belief.

Haystack Project and the RCPC oppose ICER's use of evLYG to evaluate the degree of improvement in health outcomes

ICER recently announced that it would incorporate a prominently displayed "calculation of the Equal Value of Life Years Gained (evLYG)." Haystack Project has previously expressed its concerns on the deficiencies associated with using QALY to assess value in rare and ultra-rare diseases. The evLYG corrects none of the deficiencies in QALY use across disease states (including ultra-rare diseases and rare cancers); unfortunately, it also injects its own additional set of inadequacies. In other words, it is an alternative, but in no way an improvement.

Haystack Project and the RCPC have hoped that ICER would rise to the challenge of placing patients, including those with disabilities and rare conditions, at the center of the value equation. Rather than utilize its expertise and mission to devise mechanisms to ensure that "quality of life"

is a meaningful measure for each disease state, ICER appears to have chosen to eliminate “quality” from “value” altogether. ICER’s own discussion of evLYG, and its example of two cancer treatment options – one with incremental increase in life expectancy accompanied by extreme decreases in quality of life and function – drive home the fact that the evLYG is clearly inappropriate in the context of cancer treatments, and that even ICER believes it to be so. ICER’s discussion of evLYG was accompanied by its separate assessment asserting that QALY is currently the best gauge of cost-effectiveness. We firmly believe that QALY limitations and deficiencies are most pronounced when applied to rare and ultra-rare conditions and rare cancers. We reject the concept that those limitations can be counterbalanced with an alternative approach that, like evLYG, removes the patient voice altogether.

As discussed in greater detail below, we urge ICER to reframe how it positions the patient and caregiver in deciding whether a treatment increases quality of life. This must begin with the simple question of “what do patients value?” Patients and their caregivers deserve innovation in health care economics and value assessments that rise to meet the innovations we are seeing in treating diseases that have long been untreatable and incurable.

ICER’s grafting of Quality Adjusted Life Year (QALY) metrics and a “willingness to pay” threshold onto its evaluations 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 for conditions impacting small patient populations, just as it does with all the other treatments (including blockbuster treatments) it reviews. QALYs 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) inability to consider caregiver QoL, despite the particularly profound caregiver impact within these disease states.

A comprehensive study on the use of incremental cost per QALY gained in ultra-rare disorders by Schlender 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 impede or delay access to needed treatments. Patients in countries with technology assessment approaches that use QALY and rigid willingness-to-pay criteria experience treatment delays and coverage denials, and decreased associated survival rates. Patients in the US have soundly and repeatedly rejected the foundational assumption that health care expenditures are fixed, finite, and should be used as a bar to permit or deny treatment access.

Similarly, QALY measurements may be deficient for cancer patients in three important respects: descriptions of health state, valuation, and source of values upon which measures are based.⁷

First, the measure of health-related quality of life in adults has been found to be relatively insensitive to changes in health status of cancer patients. Second, the time trade-off, often the preferred technique for estimating the values of health states, involves making assumptions that

are likely to be violated in end-of-life scenarios. Third, the practice of using valuations of members of the general population, as recommended by NICE, is problematic because individuals in the general population typically misunderstand what it is really like for patients to live with cancer.⁸ Unless ICER changes the way QALY is constructed, and includes disease-specific factors related to patient preferences, the limitations associated with QALY will continue to confound ICER's attempts to accurately capture the value of the health gains deemed important by cancer patients, particularly those with rare cancers..

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

We urge ICER to place patient and caregiver engagement at the center of its assessments. ICER should aim to gain a better understanding of the outcomes that are relevant and meaningful to patients. 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, often are not reflected by global or specific clinical measures that feed into a QALY, thus again reducing the validity of the framework in assessing value based on patient-centric outcomes.

ICER discusses outreach to patients and patient groups as part of its inquiry. Unfortunately, this outreach continues to be little more than perfunctory. It 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.

Patient advocates, armed with sufficient time to devise proactive and meaningful input, can not only improve the validity of ICER's assessments, but increase patient acceptance of and agreement on the results of its reviews. Haystack Project and the RCPC actively encourage patient advocates to explore and gather data on what outcomes are most important to patients. ICER appears uncomfortable incorporating patient priorities, preferences and views on outcomes into its QALY framework due to concerns that the resulting analysis will lack validity. Yet, there is no evidence whatsoever indicating that general population perceptions of high-value outcomes have validity across rare and ultra-rare disease states and rare cancers.

ICER should solicit and give a measure of deference to patient preferences and priorities within its value assessment. ICER could use concepts of "relative" value similar to those used by payers in setting payment amounts for services based on time and resources relative to a benchmark. For example, ICER should integrate a patient perspective report that outlines outcome priorities unique to the disease state into the preference hierarchy ICER uses to measure QALY. This would enable ICER to assign quantifiable values to disease-specific priorities, rather than relegating patient preferences to a "side bar" discussion. Any ICER concerns about the validity of such an approach should be tempered with an acknowledgement that general population-based priorities have significant shortcomings in capturing the treatment

goals and priorities of those facing rare life-threatening and life-limiting conditions.

Haystack Project and the RCPC Remain Concerned that ICER's Evaluation of Evidence Skews Against Rare Cancers and Rare and Ultra-Rare Disorders.

Haystack Project has previously urged ICER to approach its evaluation of the “quality” of evidence that takes into account the number of impacted patients and efficacy of available treatment options. Large population studies are rarely possible, randomized trial designs can raise ethical concerns, and the societal interest in getting effective treatments to these patients while the patient can benefit from them outweighs payer interest in long-term data.

We note that, in evaluating SMA treatments, ICER declared Biogen's Spinraza “low value” for the money, while simultaneously stating that:

As shown by the evidence for Spinraza, even for ultra-rare conditions, manufacturers can and should seek to conduct larger, randomized trials with long follow-up. In SMA, an ultra-rare condition with approximately 500 new cases in the US per year, Biogen conducted multiple RCTs, many of which enrolled over 100 individuals. Their efforts to generate such high-quality evidence sets a standard of excellence which other manufacturers should follow.⁹

We strongly urge ICER to incorporate sufficient flexibility into its framework to address the unique challenges associated with developing products for rare and ultra-rare conditions and rare cancers. There is clearly a serious flaw in methodology if an innovation is “low value” despite offering significant benefit to a pediatric population that will otherwise progress to disability or death, and the manufacturer's clinical program sets a “standard of excellence” with respect to evidence quality. We are concerned that ICER will hold manufacturers to this unrealistic “standard of excellence” and dismiss treatments, indications and subpopulations for which evidence is promising, but less robust, as unsupported by evidence. Moreover, the SMA patient advocacy organization had compiled a patient registry that streamlined clinical trial enrollment; for many diseases, patient registry development is both time- and resource-intensive.

We urge ICER to avoid conclusions similar to that contained in the SMA assessment with respect to SMA subpopulations, i.e., that “given the substantial remaining uncertainty regarding the benefits of initiating disease-modifying treatments in certain subpopulations, manufactures should provide treatment at no cost where evidence is lacking.” We are concerned that these conclusions, if they proliferate and are operationalized, would impede access for the rare and ultra-rare disease and rare cancer patients who are at greatest need for a treatment option.

ICER should avoid assigning value-based price benchmarks when the disease state makes it impracticable to translate patient-centered outcomes into QALY.

We urge ICER to recommit to its position 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.” Although

ICER did not adhere to these limitations in more recent reviews, for ultra-rare conditions and rare cancers, the analyses would fulfill ICER's goal of supporting informed decisions between patients and their providers.

Similarly, ICER has previously noted 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. We believe that this concept should have been applied to ICER's review of SMA treatments and to any rare cancer treatment. Haystack Project and the RCPC urge ICER to avoid evaluating these treatment options unless the methodology captures patient and caregiver impacts, priorities, and concerns.

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 challenges in applying its standards to these therapies and arriving at fair, ethical, and reasonable conclusions. An assessment purporting to be evidence-based that requires *ad hoc* methodological changes, reliance 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 health care system. Again, we urge ICER to maintain transparency and scientific integrity, provide patients and patient advocacy organizations with sufficient time to help ICER make meaningful patient-centered assessments, 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, rather than in deciding whether treatments for patients with rare and ultra-rare diseases and rare cancers have fully demonstrated "value" when they are launched..

Haystack Project and the RCPC believes the challenges to developing and marketing products for rare and ultra-rare diseases and rare cancers 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 its framework over time have yielded assessments that judge the novel treatments we hope for and need to live full and productive lives as "low value." Specifically, we believe that ICER's framework(s):

- Inappropriately conflates the impact of a therapy on patient health outcomes, including quality of life, with the potential budget impact to any individual payer or group of payers;
- Fails to consistently and transparently apply standards that are validated for use within the disease state;
- Will have the unintended consequence of discouraging innovation;

- Fails to incorporate real-world data, and pricing decisions; and
- Fails to incorporate patient and caregiver perspectives of value.

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 new treatments, even as it acknowledges that low patient populations may make traditional randomized clinical trials (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 rare and ultra-rare disease and rare cancer treatments. It will, however, inject additional risk and uncertainty for innovators considering the fiscal prudence of investing in these 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, 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, and rare cancers for which there are few, if any, potentially curative options. We continue to believe that ICER's tendency to emphasize the short-term budget impact of treatments using assumptions and arbitrary thresholds may be used as a rationale to restrict patient access.

Conclusion

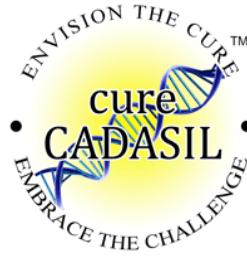
Once again, we appreciate the opportunity to comment on the proposed framework adaptation. As the voice of rare and ultra-rare disease, and rare cancer patient advocates, we look forward to working with you in the future to facilitate patient and caregiver engagement, and to further inform your rare and 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.

[See attached signatories]



HAYSTACK PROJECT: ICER FRAMEWORK COMMENT SIGN-ON





202.360.9985

Saira.sultan@haystackproject.org

<https://haystackproject.org/>



REFERENCES

¹ https://icer-review.org/wp-content/uploads/2018/12/QALY_evLYG_FINAL.pdf

² <https://smanewstoday.com/2018/08/14/nice-opposes-adding-sma-treatment-spinraza-uk-public-health-system/>

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>

⁵ Vernon A, "Examining the link between price regulation and pharmaceutical R&D investment ." *Health Economics*. 2005. 14: 1-16.

⁶ Kutjavina M. "The effect of price control threats on pharmaceutical R&D investments." (2010).

⁷ Using QALYs in Cancer: Review of the Methodological Limitations, <https://www.sciencedirect.com/science/article/pii/S2213538316300236>

⁸ Id.

⁹ https://icer-review.org/wpcontent/uploads/2018/07/ICER_SMA_Final_Evidence_Report_040319.pdf



CHAMP
Coalition For Headache
And Migraine Patients

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: Migraine Community Input for ICER's 2020 Value Assessment Framework

Dear Dr. Pearson:

On behalf of the Headache and Migraine Policy Forum (HMPF), thank you for the opportunity to provide input as ICER considers improvements to its value assessment framework for 2020. We appreciated the ability to work with ICER last year during its migraine assessment and look forward to continued interaction in the future.

HMPF recognizes that health insurers and policymakers today are increasingly committed to defining value based upon medical therapies' clinical effectiveness and rely upon groups like ICER to help make such preliminary assessments. Your ability to employ methodology that is fair, patient-focused, and comprehensive is important and we applaud your willingness to improve upon your process. HMPF asks that you remember that, more than any other stakeholder, it is patients who will feel the impact when value assessments influence health plans' formulary, coverage and cost-sharing decisions.

With that in mind, HMPF proposes the following recommendations for improving ICER's value assessment framework, both in process and substance:

PROCESS

ICER Should Allow for Both an Appropriate Disease Specialist and Disease-Impact Patient to Serve as Voting Members for All Reviews.

During the 2018 ICER Migraine Review, HMPF noted that the Voting Panel initially included an OBGYN to represent the clinician expert; upon questioning, we understand this specialist was included because migraine disease disproportionately affects women. Medical students undergo approximately *one hour* of education on *all* topics related to neurology – an insufficient amount of training required to fully understand the specialty let alone the sub-specialty of headache disorders. HMPF was appreciative that ICER recognized this concern and at least included a neurologist on the Voting Panel during its final review. However, broadly speaking, this is a continuing challenge and we would recommend ICER take a more inclusive approach by specialty with subsequent reviews for all disease states.

Similarly, we strongly request that a disease-impacted patient be allowed to serve as a member of the Voting Panel. While it is positive that ICER allows for testimony opportunities for impacted patients, designating a patient Voting Panel member with voting power would reflect a more substantial commitment to patient input. Furthermore, we request ICER commit to working with the leading patient advocacy organizations in any reviewed disease state to collaboratively select a patient representative that broadly and faithfully reflects the disease patient perspective.

ICER Should Allow More Time for Patient Groups to Respond to Various Stages of the Open Input Process.

Patient advocacy groups have substantially fewer resources than industry or ICER to evaluate and respond to open comment periods or drafts of information from ICER. To ensure that patient advocacy organizations have enough time to meaningfully participate in the ICER review process, we request that ICER extend the comment/review periods so there is more time to digest, collectively discuss and provide important patient-perspective feedback.

METHODOLOGY

The Use of the QALY in Value Assessments Impacting Chronic Diseases is Discriminatory.

We urge ICER to apply methodologically sound and clinically useful techniques – but that does not include usage of the QALY. For heterogeneous populations like migraine patients, indirect comparisons are infeasible. ICER should consider important prognostic factors, such as age, previous treatment history, baseline pain levels, and the fact that migraine attacks do not have a static start and end point, making determination of the exact number of headache days challenging to determine.

QALYs also result in lower ICER valuations for regenerative or life-enhancing therapies. We emphasize that any therapy that improves outcomes for the migraine patient population that is chronic or high/medium-episodic or poorly responds to existing therapies has tremendous value to this community.

Finally, translation of a QALY-based value assessment to coverage and access has been found to be discriminatory against people with disabilities by the U.S. Department of Health and Human Services.¹ Migraine patients are more than twice as likely as those not living with migraine disease to be disabled.² Applying a single rigid framework across many chronic diseases is therefore problematic and should be adjusted or disregarded in favor of usage of the DALY for certain diseases.

ICER Should Give Substantial Weight to Real-World Evidence in its Quantitative Review.

Clinical trials data is important but represents a narrow set of information currently used by ICER in its value assessments – leading to an incomplete picture about the net health benefit (or not) of a particular therapy. ICER should instead provide a more comprehensive evaluation within its quantitative model that includes data relating to the societal burden of disease including the effects of inhibited productivity and absenteeism as well as expected reduction of costly ER visits associated with preventive therapy use. Data that includes patient experience is of particular interest to persons living with migraine and other chronic diseases. Burying this information in the qualitative section of the Final Report means that this type of data is not meaningfully considered by ICER and discounts the patient and provider perspective.

For example, over the past six years Migraine.com has conducted a large national survey called *Migraine in America*, which poses questions of people with migraine disease and provides unique insights into quality of life issues for migraine patients.³ The 2017 edition included responses from more than 4,500 Americans to 110 questions that spanned the full breadth of the migraine experience, providing a rich and up-to-date view into what it means to live with the disease.

Likewise, where certain disease states (like migraine) *exist on a spectrum*, ICER should consider additional data that shows a clear distinction within the subgroup of certain chronic conditions. For example, patients who experience a high frequency of episodic migraine (headache days of 10-14 per month) are poorly reflected when pooled within either the episodic (fewer than 14 days) or chronic (15 days or more) categories. There also exists a substantial burden attributable

¹ Sullivan, Louis W. M.D. Secy. of Health and Human Services, Washington, (Aug. 13, 1992). Oregon Health Plan is Unfair to the Disabled, *New York Times*. Retrieved at <http://www.nytimes.com/1992/09/01/opinion/1-oregon-health-plan-is-unfair-to-the-disabled-659492.html>

² Steiner, Tim, et.al, Headache Disorders Are Third Cause of Disability Worldwide, *J Headache Pain*. 2015; 16: 58. Retrieved at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4480232/>; Also: http://www.pipcpatients.org/uploads/1/2/9/0/12902828/pipc_white_paper_-_measuring_value_in_medicine_-_uses_and_misuses_of_the_qaly.pdf

³ Migraine in America 2017. (2017) Migraine.com. [Survey of more than 4,500 individuals currently diagnosed with migraine to better understand their symptoms, life impact and treatment experience]. Unpublished data.

to episodic headache where patients are not symptom free in-between attacks.⁴ This is currently not reflected accurately in ICER reviews.

ICER Value Assessments Should Consider the Beneficial Cost Impact of Reducing Co-Morbid Conditions Where There is a Substantial and Interrelated Linkage to the Disease Impacted by the Therapy Under Review.

ICER's cost assessment must consider the cost impact of any reduction of co-morbid conditions that would be positively impacted by a therapeutic option for an interrelated condition. For example, while medical costs for treating chronic migraine were estimated at \$5.4 billion in the United States in 2015, total costs associated with migraine and co-morbid conditions *exceeded \$40 billion*.⁵ Research has shown that migraine disease is linked to both depression and anxiety, with up to 80 percent of chronic migraine patients exhibiting symptoms of depression.⁶ In fact, persons living with migraine are about five times more likely to develop depression than someone without migraine. Further, depression is associated with worsened migraine-related disability and reduced quality of life – even suicide. For many, depression or anxiety begins months or years after their migraine attacks start—partially because migraine can be so debilitating. Therefore a reasonable extrapolation of the cost impact of related co-morbidities must be factored into the value assessment.

ICER Should Recognize the Reality of a Multi-Modal / Combination Therapy Approach for Certain Chronic Diseases.

The reality for many patients with chronic diseases like migraine is that they will be using therapies in combination to further reduce symptoms (or headache days). When ICER assesses one therapy in a vacuum, it cannot discount the fact that a therapy, when used with another, may for example help a patient move from a “chronic” to “episodic” category, thereby increasing the quality of life for a person living with migraine disease and therefore substantially increasing *both* therapies' overall value.

Thank you in advance for your consideration. If you have questions or if we can provide further information, please contact Lindsay Videnieks, Executive Director of the Headache Migraine Policy Forum at (202) 299-4310 / Lindsay@headachemigraineforum.org or Kevin Lenaburg, Executive Director of the Coalition For Headache and Migraine Patients at (202) 365-7473.

⁴ Lampl et al, “Interictal Burden Attributable to Episodic Headache: Findings from the Eurolight Project,” Journal of Headache and Pain, Feb. 2016.

⁵ Id.

⁶ The Link Between Migraine, Anxiety, and Depression, American Migraine Foundation May 2, 2018 available at: <https://americanmigrainefoundation.org/resource-library/seeking-patient-input-for-new-migraine-medication/>

June 10, 2019

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

RE: ICER Seeks Public Input for 2020 Value Assessment Framework

Dear Dr. Pearson:

The Innovation and Value Initiative (IVI) appreciates the opportunity to offer comments on the Institute for Clinical and Economic Review's (ICER) value assessment framework.

IVI is a non-profit research organization whose mission is to advance the science and improve the practice of value assessment in healthcare by adapting a more collaborative, open and tailored approach to examining value, exploring new methods and building models that can support flexible decision making.

Prior to offering specific comments on ICER's value assessment methods and procedures, we believe it's important to recognize some degree of misalignment between ICER's approach and the unique characteristics of the U.S. healthcare marketplace that ICER's assessments are intended to influence.

The U.S. health system is highly decentralized and composed of many different stakeholders facing difficult, and often overlapping, decisions. Furthermore, decision-makers within each group are highly diverse, and all of these decisions are made in different contexts, under unique constraints and conditions. Consistent across decision-makers is the goal of identifying options that provide the most value under their own unique conditions. Approaching value assessment with a focus on one "best" answer – in this case, using the conventional cost-effectiveness and budget impact analysis conducted from a generalized health system perspective under ICER's existing value framework – ignores the reality that different stakeholders have different criteria to assess value. Value assessment should be approached from the frame of those individual decision contexts, using multiple models and methods that can support such flexibility and multi-dimensional analysis.

A further challenge exists regarding the need for a long-term view when quantifying the value of a medical technology and the frequent short-term budget-driven perspective of decision making. We agree that the long-term value of a therapy is the most important consideration, and this is certainly true for patients, their families, and society at large. In a system where health plans make coverage decisions based on short-term budget impacts, however, there is little incentive for insurers and others to prioritize investments in therapies with higher short-term costs but

greater long-term value. This issue is acknowledged and discussed in the existing ICER value framework. We are concerned, however, that merely listing long-term value alongside short-term budget impact leaves the decision-maker with the easy option to ignore long-term value. The potential disincentives to invest in treatments with long-term societal benefits are a pressing issue that confronts our society as whole, but through the reports and policy analyses produced by ICER, there is an opportunity to educate audiences on the issue and generate discussion about potential solutions.

To deliver credible and relevant information about value to U.S. healthcare decision-makers, value assessment must:

- Provide flexible models that can be fit to diverse contexts and updated as evidence evolves;
- Be totally transparent to all stakeholders;
- Explicitly acknowledge and address uncertainty;
- Incorporate non-clinical attributes and outcomes in value estimates; and
- Actively take a patient-centered focus throughout all stages of the research to assess the value of medical technology.

The following comments expand upon these issues.

Embrace Transparency by Moving Value Assessments to Open-Source Environment

As discussed above, vastly different stakeholders make healthcare decisions in equally diverse contexts, based on their own unique preferences and constraints. All of these decisions are informed by some level of value assessment, but every decision stands to benefit from rigorous, credible, and relevant information on value that applies to their specific decision, to the greatest extent possible.¹

Given the lack of consensus about the appropriate framework, modeling approaches, and relevant evidence among different stakeholders (i.e. patients, insurers, and providers), it is important to move all value assessment into a transparent, open-source environment.¹⁻³ While ICER has taken important initial steps in this regard, including providing manufacturers with limited access to cost-effectiveness models during the review period, further commitment to full transparency and open access is needed. We strongly recommend that ICER provide complete *public* access to models, underlying data, and other materials. By taking this step, ICER would make important progress toward allaying stakeholder concerns and engaging in a constructive discussion about methods.

Expand evaluation of uncertainty in estimates of value beyond parameter uncertainty and acknowledge structural uncertainty

While ICER's value assessment framework accounts for sensitivity and scenario analysis, we are concerned by the tendency to understate the degree of uncertainty in analyses/estimates and the potential impacts on decision making.

Both parameter and structural uncertainty are important to consider when evaluating the value of a medical technology. Methods for examining the impacts of uncertainty are available for parameter uncertainty – probabilistic sensitivity analysis, for example – but the impacts of structural uncertainty are more challenging to measure. This does not mean that they should be ignored, however. In previous research, IVI examined the impact of structural assumptions using the IVI-RA value model,^a in which 384 different model structures are possible,⁴ to assess the impact of structural assumptions on CEA outcomes. For a set of 32 sets of structural assumption, created based on the possible combinations of four factors^b, the authors generated incremental cost-effectiveness ratios for sequential treatment with biologic disease-modifying anti-rheumatic drugs (DMARDs), relative to conventional DMARDs. The results (see *Figure 1*) illustrate the potential impacts of structural uncertainty on cost-effectiveness results, and therefore for decision-making – indeed, if a threshold of \$150,000 per QALY gained is adopted for decision-making, basic structural assumptions could determine whether the intervention is considered cost-effective.⁵

We recognize that it is impossible to model, or even discuss, all of the possible modeling structures and assumption sets that are possible for a given analysis, but acknowledgement and some exploration of the issue is needed in assessments conducted by ICER. ICER's current approach does include a discussion of uncertainty in the evidence, which is an important first step.

The impacts of both parameter and structural uncertainty should be explicitly and thoroughly addressed in ICER reports. We recommend that all reports include a section with detailed assessment and discussion of the impacts of uncertainty on modeling, including structural uncertainty and the potential impacts of assumptions made.

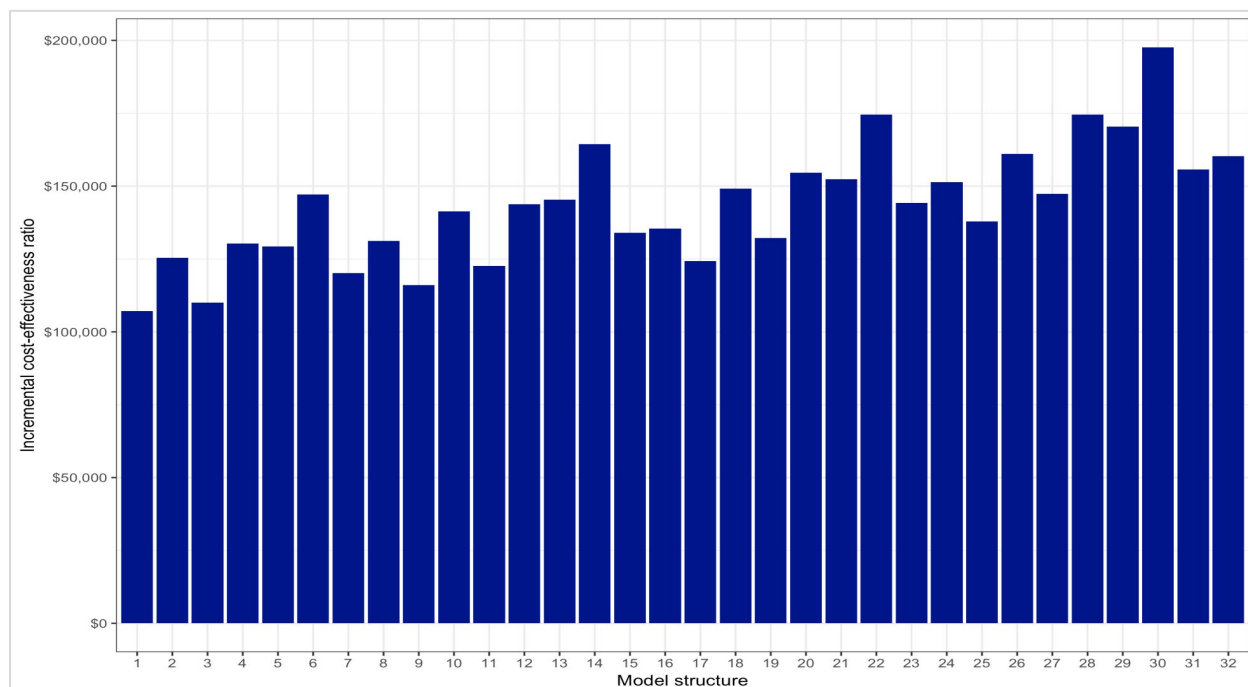
^a The IVI-RA model is an open-source individual patient simulation model for simulating outcomes and estimating value of sequences of biopharmaceutical therapies in moderate to severe rheumatoid arthritis. The IVI-RA model is part of IVI's Open-Source Value Project. For more information or to access the model, visit <https://www.thevalueinitiative.org/ivi-ra-value-model/>.

^b Four structural factors were varied:

- Impact of treatment on HAQ: 1) Treatment->ACR->HAQ; 2) Treatment->ACR->EULAR->HAQ; 3) Treatment->HAQ
- Pathways for treatment switching: 1) ACR->switch; 2) ACR->DAS28->switch; 3) ACR->EULAR->switch; 4) DAS28->switch
- Progression of HAQ in the absence of efficacious treatment: 1) constant rate of progression; 2) non-linear development with latent class growth model
- Utility: 1) Mixture model by Hernandez-Alava et al (2013); 2) Wailoo et al (2006)

For more information on these structural factors, see: Incerti D, Jansen J. A Description of the IVI-RA Model v1.0. 2017. <https://innovationvalueinitiative.github.io/IVI-RA/model-description/model-description.pdf>.

Figure 1: Sensitivity of IVI-RA model cost-effectiveness findings to 32 competing structural assumptions



Improve Incorporation of Non-Clinical Attributes

Regardless of the underlying cost-effectiveness model or perspective ICER chooses, we urge efforts to improve the incorporation of factors that are not generally captured in conventional cost-effectiveness analysis but may be important when evaluating the value of medical technology.

Since the last ICER value framework update, ICER has begun taking steps to better communicate the “potential other benefits and contextual considerations” that may impact the value of therapies and, ultimately, coverage decisions. IVI commends ICER for these efforts.

ICER’s current approach to these factors is insufficient, however. In the current approach, these non-clinical factors are briefly described in ICER reports and voted on by the reviewing Council prior to release of the final report. These factors are not reflected in the substantive results that are the focus of readers, however, and are only accounted for in value judgements through Council votes when treatments’ incremental cost-effectiveness results fall between \$50,000 and \$175,000 per QALY in “base case” analysis.

Non-clinical outcomes are currently excluded from ICER analyses because of a lack of commonly accepted practices for measuring and accounting for these elements, and also due to lack of or uncertainty in the evidence needed to parameterize them. While we agree that value



assessment should reflect the most accurate and reliable evidence possible, the exclusion of these important non-clinical dimensions is itself an assumption that affects results – essentially, the structural assumption that the impact of these factors on costs or benefits is zero. While attempting to incorporate these dimensions introduces uncertainty, so does their exclusion.

IVI recommends that ICER expand modeling efforts and analyses to incorporate additional non-clinical factors, even where methods are developing or imperfect, and where evidence is currently lacking. These analyses need not be presented as primary results, but they should serve to both illustrate their potential impact on value and highlight areas where improved methods and evidence are needed.

Where these parameters are quantifiable, it is particularly important that ICER endeavor to explicitly incorporate these attributes into analyses. For example, lost wages due to absenteeism or additional costs for treatment-related lodging and transportation should be considered. Patient preferences for treatment attributes such as mode and frequency of administration should also be explicitly addressed. In addition, capturing heterogeneity in preferences may be of interest.

To support this expansion to include non-clinical factors, ICER should seek partners in the patient and research communities. For example, a small-scale study with patients could be used to generate preliminary data on the impacts of changes in clinical measures or side effects on caregivers, which could then be linked to individual therapies' relative effects to compare caregiver impact across therapies. Such a study could be conducted in partnership with an existing patient group or research institution.

Again, we appreciate your willingness to invite comments on ICER's current value assessment framework and hope we have offered substantive recommendations that enhance your organization's methods and models.

Sincerely,

A handwritten signature in dark ink, reading 'Jennifer L. Bright'.

Jennifer Bright, MPA
Executive Director

References

1. Jansen JP, Incerti D, Curtis JR. Toward Relevant and Credible Cost-Effectiveness Analyses for Value Assessment in the Decentralized U.S. Health Care System. *Journal of Managed Care & Specialty Pharmacy*. 2019;25(5):518-521.
2. Jansen JP, Incerti D, Linthicum MT. An Open-Source Consensus-Based Approach To Value Assessment. *Health Affairs Blog*. 2017.
<https://www.healthaffairs.org/doi/10.1377/hblog20171212.640960/full/>.
3. Hay JW. Now Is the Time for Transparency in Value-Based Healthcare Decision Modeling. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2019;22(5):564-569.
4. Incerti D, Jansen J. A Description of the IVI-RA Model v1.0. 2017.
<https://innovationvalueinitiative.github.io/IVI-RA/model-description/model-description.pdf>.
5. Incerti D, Curtis J, Lorenzi M, Jansen J. Exploring Structural Uncertainty With An Open-Source Cost-Effectiveness Model For Rheumatoid Arthritis. *Value in Health*. 2017;20(9):A751.



**Institute for
Patient Access**

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.

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,

A handwritten signature in black ink, appearing to read "Brian Kennedy".

Brian Kennedy
Executive Director

June 10, 2019

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

RE: *ICER's 2020 Value Assessment Framework*

Dear Dr. Pearson:

On behalf of Intercept Pharmaceuticals, Inc., I appreciate the opportunity to provide comments on ICER's 2020 Value Assessment Framework. As a biopharmaceutical company dedicated to developing innovative treatments for progressive, non-viral liver diseases, we are strong supporters of rigorous, patient-centric value discussions and applaud ICER's efforts to elicit feedback in a timely manner.

Intercept is working to address conditions with great unmet need. Our therapeutic areas of focus often lack the robust epidemiological data required for calculations within the ICER value framework. This is particularly the case for orphan conditions such as Primary Biliary Cholangitis (PBC) and for poorly recognized conditions such as Non-alcoholic Steatohepatitis (NASH). Managing uncertainty within these types of diseases, particularly as a treatment moves from clinical trials to real world clinical practice, represents an important challenge for both the calculation of Long-Term Value for Money and Short-Term Affordability — the pillars of the ICER value assessment framework.

We agree in principle with ICER's approach of looking at "short-term" budget impact over a five-year time horizon; however, payers often define "short-term" as one or two years, which makes the accuracy of ICER's budget impact analysis critically important. These time horizon/data insufficiency considerations do, however, increase the difficulty in the calculation, when epidemiological estimates of incidence/prevalence and diagnosis rate are uncertain and highly variable. Further, the introduction of a treatment for a condition where no current treatment exists will change physician and patient behaviors in the short-term in unpredictable ways. Overestimates of short-term budget impact for payers will inaccurately capture the value that these treatments will bring and could negatively impact patients' access to novel therapies that are potentially curative or can profoundly improve patient survival and impact morbidity.ⁱ

We appreciate ICER's desire to model short term affordability and budget impact in advance of the commercialization of new interventions and acknowledge that ICER has made important changes to its budget impact model as part of the previous value assessment framework update. As noted in the ICER framework, budget impact analyses do inform very real short-term decisions by payers about how to allocate resources within a given budget year. However, ICER's current approach uses an inappropriately flat calculation of patients eligible for treatment based on disease prevalence and label indication, phased in equally over five years, assumptions that seem unlikely to be true in a condition presented with new treatments and major therapeutic changes. Empirically, we know that the uptake of new therapies is highly variable, depending on everything from physician and patient education to payer utilization management policies and cost-sharing.ⁱⁱ Rarely, if ever, would it be uniform across a five-year time horizon.

In the next iteration of ICER's value assessment framework, we propose that ICER adopt a more dynamic approach to more accurately model anticipated clinical use and offer the following three recommendations:

1) ICER should distinguish between diseases that have different levels of understanding of disease etiology and pathophysiology based on current medical science.

As our understanding of disease evolves from symptom phenomena, to pathological mechanisms, to an understanding of disease etiology, treatment philosophy and urgency will change. In the case of infectious diseases, where the infectious agent is etiological and treatment will likely result in a 'cure,' treatment of all patients as quickly as possible would be the goal and easily understood. In the case of rare diseases, patients and healthcare providers may require significant education or specialty diagnostics, which can delay uptake even when a new treatment is commercially available.ⁱⁱⁱ Chronic conditions—where medical science does not either fully understand the etiology or no 'cure' exists—present a completely different challenge to forecasting budget impact: uncertainty around diagnosis rates, treatment success, when and who to treat, impact of co-morbid conditions, disease time course, are all variables that are often poorly understood and difficult to quantify.^{iv,v} Intercept believes these variables strongly influence and increase the uncertainty of forecasting budget impacts.

2) ICER should apply relevant historical uptake analogues.

We recommend that ICER apply treatment uptake analogues from diseases with characteristics of uncertainty that are similar to the target therapeutic for which the budget forecast is being undertaken. These characteristics include: disease of unknown etiology, no common diagnostic paradigm, no current pharmacological treatment, etc. This approach may be very valuable to better gauge how patients, providers, and payers will react to the commercial availability of new treatments. The search for such analogues should not be limited to the therapeutic area of the putative target for the calculation.

3) ICER should incorporate feedback on anticipated use from treating clinicians.

To include more robust patient perspective in its reviews, ICER has started to work with patient advocacy organizations to solicit patient-generated data and feedback. For example, as part of the recent Secondary Progression Multiple Sclerosis (SPMS) review, ICER worked with the Multiple Sclerosis Coalition to conduct an online survey of MS patients.^{vi} We recommend ICER take a similar approach with clinicians, including working with professional medical societies and associations to survey physicians about how they learn and make prescribing decisions. Understanding how clinicians intend to utilize the drug or intervention, including their benefit/risk assessment, would provide a more informed perspective of the likely treated population rather than basing estimates of prescribing solely on the clinical trial inclusion criteria.

While the budget impact analysis is only one component of ICER's value assessment framework, it has the potential to profoundly influence treatment access and patient cost sharing. We strongly believe that these adjustments would significantly improve the accuracy, relevance and usefulness of ICER's potential budget impact analysis for all stakeholders, most notably payers and policymakers.

Sincerely,

Bruce Wong

Bruce Wong MD, MSc, FRACP
Vice President, Medical Affairs Research
Intercept Pharmaceuticals, Inc.

ⁱ Broder, M. S., Zambrano, J. M., Lee, J., & Marken, R. S. (2017). Systematic bias in predictions of new drugs' budget impact: Analysis of a sample of recent US drug launches. *Current Medical Research and Opinion*, 34(5), 765-773. doi:10.1080/03007995.2017.1320276

ⁱⁱ Lubl6y  . (2014). Factors affecting the uptake of new medicines: a systematic literature review. *BMC health services research*, 14, 469. doi:10.1186/1472-6963-14-469

ⁱⁱⁱ Valdez, R., Ouyang, L., & Bolen, J. (2016). Public Health and Rare Diseases: Oxymoron No More. *Preventing chronic disease*, 13, E05. doi:10.5888/pcd13.150491

-
- ^{iv} Bernell, S., & Howard, S. W. (2016). Use Your Words Carefully: What Is a Chronic Disease?. *Frontiers in public health*, 4, 159. doi:10.3389/fpubh.2016.00159
- ^v Vogeli, C., Shields, A. E., Lee, T. A., Gibson, T. B., Marder, W. D., Weiss, K. B., & Blumenthal, D. (2007). Multiple chronic conditions: prevalence, health consequences, and implications for quality, care management, and costs. *Journal of general internal medicine*, 22 Suppl 3(Suppl 3), 391–395. doi:10.1007/s11606-007-0322-1
- ^{vi} *Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value*(Rep.). (2019, May 2). Retrieved June 4, 2019, from Institute for Clinical and Economic Review (ICER) website: https://icer-review.org/wp-content/uploads/2018/10/ICER_MS_Evidence_Report_050219.pdf

ISPOR responses to specific aspects of ICER's value framework updates, 6/10/2019

4. Other Benefits or Disadvantages and Contextual considerations

We encourage ICER's plan to continue consideration of contextual factors of value in a pilot fashion. In its recent report, ISPOR's Special Task Force on US Value Assessment Frameworks encouraged consideration of many of these same "novel" elements of value, as well as the deliberative processes that could help enable their use in decision-making, while also acknowledging that they generally need further research and testing (Lakdawalla et al, 2018; Phelps et al, 2018; Garrison et al, 2018). We note a few things, however. Your set of potential elements does not include the aspect that is often termed the "value of hope," ie, the situation where a therapy may not help a majority of patients (so it doesn't improve median survival), but does significantly help, or cure, some proportion of patients – the "thick tail" phenomenon. It has been shown that patients show significant willingness to pay for that feature of therapy, and ASCO has included that consideration in its value framework (Shafrin et al, 2017). Another value element not directly mentioned is the value of risk protection, though that value does seem to be highest for diseases with a high burden of illness, a factor that you do include (Lakdawalla et al, 2017). In many cases these factors can be quantified in an augmented cost-effectiveness analysis or net monetary frameworks; it may be useful to build up a set of case examples here to learn more about them. We would also recommend reconsideration of piloting an MCDA-like approach to help quantify the influence of such factors – while those weights can vary by approach, such processes can provide insight into the relative importance of those factors. Finally, the Second Panel on Cost-Effectiveness in Health and Medicine provides an "Impact Inventory" which should serve as a reference point for other types of societal benefits (eg, educational, legal) in selected cases.

6. Report Development

While this comment may go beyond the current bounds of the "Report Development" part of your value framework, we believe there is another scientific aspect of your report development process that merits discussion, even though it is also related to the scoping process described in other ICER documents.

Specifically, ICER typically starts their process in their "scoping" phase with an existing disease state model in mind (in part, presumably, because the evaluation process can be done more quickly if based on an existing model). However, there may be situations where novel, new treatments have a significant impact on patient outcomes and mortality through a mechanism that is not considered in the existing model, so a new or revised model is warranted to properly evaluate the new treatment. This information comes out in the manufacturer interactions during the scoping phase and in the manufacturer's comments to the Scoping draft. The challenge for ICER and the modeling team is that their standard timelines are based on the assumption that they will use an existing model. We would suggest, given an important priority being the

relevance and accuracy of the model being used for evaluation, that it would be helpful to get input as early as possible on whether ICER has the right model for the novel, new treatments BEFORE the draft Scoping document ... and/or build in some flexibility with respect to report development timelines.

7. Patient Engagement

With regard to this section and ICER's efforts to include patients and the public in the value assessment process, we commend ICER for directly addressing this important component of value assessment. We recommend that ICER continue to build upon the vehicles for incorporating patient input into the value assessment process, recognizing and honoring that patients with critically important perspectives are not necessarily well-grounded in the concepts of health economics, or even in the existence of ICER as a body. It is imperative that communication and outreach efforts are co-designed by patient partners, to ensure that they are understandable and relevant to patients. We also suggest that, just as highlighting in the Draft Evidence Report indicates where changes have been made *based on* patient and other input, it would be incredibly useful to highlight areas where patient input was collected but did not change the end result, and why that was the case, including a discussion about the nature, construct, and source of the PGHD and what the assessors found lacking. Finally, providing well-advanced notice to patients and facilitating travel for patients to attend in-person meetings is important. Without assistance, only patients with financial resources will be able to attend and the discussion will lack a critical voice—particularly within the ambit of a cost conversation.

8. Identification of low-value services as part of evidence review process

In general we agree with and encourage this approach. Of course, there are some guideposts here, as expressed in our Special Task Force Report (Willke et al, 2018):

“An efficient way to address budget constraints would be to reduce spending on, or to replace, technologies with less favorable cost-effectiveness ratios in favor of budget-expanding but more cost-effective technologies. This could be achieved by price reductions on new technologies, by utilization management targeting less cost-effective subgroups of patients, or by disinvestments in less cost-effective treatments. A lower cost-effectiveness threshold could be set (given some uncertainty about pending new treatments and the success of price reduction and other efforts) that would help achieve the needed overall budget [32]. Any new products (including the new budget-expanding technology in question) as well as existing technologies that could be subject to disinvestment, could be held to that new standard. Ideally, an affordability strategy should examine the entire medical care portfolio subjecting all technologies to the same opportunity cost criterion, rather than assuming that budget savings can be achieved by restricting the price or utilization of technologies that meet the affordability criteria.

Barriers to reducing price or to disinvestment include high transaction costs associated with reducing the use of established technologies within health systems and equity concerns if the technologies of interest are the only effective options for patients with specific conditions.”

Ideally, one would be able to utilize real world costs and outcomes for existing technologies to identify those services that have turned out to be low value in practice. Over time, use of some technologies may evolve to their most efficient uses relative to initial approval, or, by contrast, spread too widely to largely inefficient uses, and prices often change after initial studies are done. We realize that such studies are not done as much as they should be, and in the absence of randomization, careful analysis is necessary, so reliable real-world evidence may not be easily available, but we encourage consideration of real-world evidence when feasible.

References

Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining elements of value in health care—a health economics approach: an ISPOR Special Task Force report [3]. *Value Health* 2018;21:131–9.

Phelps CE, Lakdawalla DN, Basu A, Drummond MF, Towse A, Danzon PM. Approaches to aggregation and decision making—a health economics approach: an ISPOR Special Task Force report [5]. *Value Health* 2018;21:146–54.

Garrison LP, Neumann PJ, Willke RJ, et al. A health economics approach to US value assessment frameworks—summary and recommendations of the ISPOR Special Task Force report [7]. *Value Health* 2018;21:161–5.

Shafrin, J., Schwartz, T.T., Okoro, T., and Romley, J.A. Patient versus physician valuation of durable survival gains: implications for value framework assessments. *Value Health*. 2017; 20: 217–223.

Lakdawalla D, Malani A, Julian R. The insurance value of medical innovation. *Journal of Public Economics* 2017; 145:94-102.

Willke RJ, Neumann PJ, Garrison LP, Ramsey SD. Review of recent US value frameworks—a health economics approach: an ISPOR Special Task Force report [6]. *Value Health* 2018;21:155–60.

June 10, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Public Input for 2020 Value Assessment Framework

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson:

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we believe meaningful transparency is a positive step toward a more sustainable, results-based health system that delivers greater access to care in a more efficient manner. We take a responsible [approach](#) to pricing that recognizes our dual obligation to patients today, who need access to our medicines, and patients tomorrow, who count on us to deliver cures and treatments for the most challenging and intractable diseases. In that spirit we welcome [ICER's call for suggestions](#) to improve its value assessment framework.

Our comments below are rooted in our **principles for assessing the value of our medicines**, as outlined in our annual [Janssen U.S. Transparency Report](#):

- What matters most in determining a medicine's value is its impact on patients.
- The value of a medicine includes its impact on the healthcare system and society.
- Treatment outcomes should be assessed over an appropriate timeframe to capture all the benefits and risks for patients, the healthcare system, and society.
- Evidence considered in assessing the value of a medicine should be high-quality, current, and relevant.

Thus, we offer the following suggestions to improve ICER's value framework:

- I. ICER should focus its efforts on the overall healthcare system to better achieve a "more effective, efficient and just health care [*sic*] system," per ICER's stated principles ([Ref.](#), accessed June 3, 2019).
- II. The evaluation process should be rigorous, robust, and equitable for all people and organizations that are involved or may be affected.
- III. ICER's meetings should allow adequate time for stakeholder comment.
- IV. Evaluation methods should be based on the highest scientific standards.

We develop these suggestions below.

I. Focus on Overall Healthcare System

ICER's declared aspiration, per its guiding statement ([ref.](#), accessed June 3, 2019), is "to translate...evidence into policy decisions that lead to a more effective, efficient and

just health care system.”

However, ICER mainly focuses on prescription drugs—a segment of the healthcare system that represents approximately 14% of US spending.¹ It largely ignores costs in the rest of the system. If ICER is to achieve its goal of creating “a more effective, efficient and just health care system,” it should expand its focus to other areas of the healthcare system.

II. Include Multiple Voices in a Rigorous Process

ICER’s entire value assessment process should be transparent and balanced. It should encourage robust public debate. Analyses should be subject to peer review and be fully reproducible. All aspects of the process, from topic selection to final report and eventual public statements, should reflect these standards so that ICER is providing the clearest direction to all healthcare decision makers, including patients, care-givers, providers, employers, payers, and suppliers.

This is critical, because ICER is advocating that health systems use these reports and make decisions about access to medicines that will have a profound impact on patient choice and health.

ICER should also make every effort to incorporate the voices and concerns of patients and caregivers into all aspects of its process. (After all, improving patient health is the ultimate goal.) ICER should solicit patient perspectives early on and explicitly include those perspectives in its analyses: for example, by adding patient-reported outcomes and indirect costs into the base-case economic evaluations, especially those that are most important to patients, such as productivity.

Topic reviews and calls for comments by ICER require significant time on the part of suppliers to ensure ICER has the most relevant evidence. It is unfortunate that ICER appears to take advantage neither of FDA’s significant expertise nor of the thorough evaluations the agency conducts in determining whether to approve products’ uses, dosing, safety, and efficacy.

III. Create Conditions for Meaningful Debate

Regarding ICER’s public meetings, we offer three suggestions to allow more meaningful input.

- The meetings should provide adequate time for voting members and the public to comment, ask questions, and absorb the significant amount of information provided at meetings. We note that the very limited time currently allotted for comment – five minutes per speaker – leaves the impression that giving speaking time to manufacturers is a pro forma gesture backed by no genuine intention to take their comments into account.
- Comment periods should be extended to allow all interested parties enough time to respond comprehensively.

- The patients, clinicians, and health economists who are voting members should have appropriate experience and direct, recognized disease-area expertise.

IV. Keep Methods Sound and Current

There are several ways that ICER can improve its methods. Overall, ICER should strive to adhere to the highest standards of evidence and economic evaluation.

- ICER should attempt to incorporate as many relevant factors into its recommendations as possible.
- ICER should reduce reliance on singular and limited measures such as quality-adjusted life years (QALYs) and investigate explicit use of multiple criteria decision analysis (MCDA), which more accurately reflects the nuanced and multi-faceted nature of healthcare value.
- At every stage of its evaluations, ICER should include all relevant outcomes, including clinical outcomes, patient-reported outcomes, and societally important outcomes such as productivity and caregiver burden.
- ICER should ensure appropriate and complete assessments of all evidence, from randomized clinical trials to real-world evidence. It should also consider the limitations of each type of evidence. For example, off-label claims should not be included in ICER reviews because these uses are not approved by the FDA.
- We urge ICER to recognize the known limitations of cost effectiveness analysis (CEA) and ensure that any economic evaluation meets the highest external standards, such as those of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). For example, ICER primarily uses a payer perspective in its CEA base-case analyses, despite the fact that most major CEA guidelines recommend using a societal perspectiveⁱⁱ. Choosing to focus on the payer's perspective while ignoring important other costs and benefits will lead to an inefficient allocation of resources over both the short and the long term.ⁱⁱⁱ Additionally, this may lead to underinvestment in products that have large social benefits in favor of products which meet payers' needs but have lower overall social value. For example, curative therapies are likely to provide significant overall benefits but may be underutilized because of ICER's focus on the payer's perspective. Valuations informed from a societal perspective are more likely to benefit all stakeholders, in the short and long term.
- ICER should eliminate its "Budget Impact" assessment. ICER suggests that this portion of the assessment is designed to highlight "affordability" concerns about certain products. However, ICER's analyses do not provide information that is specifically relevant to individual decisionmakers and their budgets.
- ICER's use of incremental cost-effectiveness and affordability thresholds is problematic. The use of discrete thresholds and aggregate estimates of cost-effectiveness ignores patient-level heterogeneity in both disease severity and

treatment effectiveness. Even more important, ICER's use of thresholds puts an arbitrary cap on the value of human life. Currently, for most interventions, ICER compares the estimated cost-effectiveness ratio to thresholds that range from \$50,000 to \$150,000 per QALY. This suggests that interventions whose cost-effectiveness ratio exceeds \$150,000 per QALY are not valuable—and places a monetary limit on the lives of patients who may benefit from those interventions.

V. Improving Methodology is Not Enough

We urge in conclusion that while fixing the shortcomings of value frameworks can help bring meaningful transparency to our healthcare system, a critical question remains unaddressed: namely, who is best equipped to make decisions about healthcare and the value of a life. At Janssen, we believe those decisions ultimately belong to patients, their families, and physicians.

Sincerely,



Anastasia G. Daifotis, MD
Chief Scientific Officer
Janssen Pharmaceuticals
North America

ⁱ Altarum Institute, Center for Sustainable Health Spending Data Brief. "A Ten Year Projection of the Prescription Drug Share of National Health Expenditures Including Non-Retail." 2014 & Addendum update August 2015. http://altarum.org/sites/default/files/uploaded-publication-files/Non-Retail%20Rx%20Forecast%20Data%20Brief_with%20Addendum.pdf.

ⁱⁱ Neumann, P.J.. Costing and Perspective in Published Cost-Effectiveness Analysis, *Med Care* 2009; 47: S28-S32.

ⁱⁱⁱ Jonsson, B. Ten arguments for a societal perspective in the economic evaluation of medical innovations, *Eur J health Econ* (2009) 10: 357.

Response to the Institute for Clinical and Economic Review 2020 Value Framework update

Aris Angelis, PhD, Panos Kanavos, PhD, Lawrence D Phillips, PhD
London School of Economics and Political Science (LSE)

Introduction

We are taking this public consultation opportunity for the 2020 update of the Institute for Clinical and Economic Review (ICER) Value Assessment Framework to comment on the fourth point of the consultation invitation document which focuses on the methods by which benefits are integrated, i.e. relating to contextual considerations and other factors relevant to judgments of an intervention's value. Our points correspond to the "Overview of the ICER value assessment framework and update for 2017-2019" document.

To begin with, we would like to acknowledge the existence of different methods for the purpose of assessing the value of new health technologies as part of health care evaluation, an interdisciplinary scientific field also known as Health Technology Assessment (HTA). As part of current HTA practices, a number of value assessment approaches are used across different jurisdictions, which could be broadly divided into (a) clinical benefit assessment, (b) economic evaluation and (c) value based assessment. Different methods can serve different needs and therefore can satisfy to a different degree different decision-makers' requirements. We perceive the ICER methodology to pertain to the "value based assessment" group of methods having as a mission to serve the needs of decision-makers interested in measuring interventions' benefits that go beyond their clinical value and cost effectiveness, aiming to capture other aspects of value as part of a more comprehensive approach. This group of approaches is not yet characterized by a single or specific type of methodology, but most approaches so far have emerged on the grounds of economic evaluation's inadequacy to capture the multi-dimensional nature of new medicines' value in a structured and consistent way. Examples include the fluctuating Incremental Cost Effectiveness Ratio threshold in England based on additional value concerns relating to end of life criteria that can effectively increase the valuation of a unit of health outcome for terminal illnesses, or the fluctuating threshold in Sweden based on disease severity or need.

Decision Analysis and MCDA

We believe that the potential usefulness of decision analytic approaches for measuring the overall value of health care interventions, including aggregating different benefit components, have not been fully

realized by ICER. Although also evolved out from Expected Utility Theory, this type of approaches represents an alternative way of thinking to economic evaluation. Probably the most relevant theoretical framework relevant to value measurement relates to Decision Theory, with this applied discipline of Decision Analysis acting as the practical instrument of analysis.

Raiffa, first defined the spirit of Decision Analysis as “divide and conquer: decompose a complex problem into simpler problems, get one’s thinking straight on these simpler problems, paste these analyses together with logical glue, and come out with a program of action for the complex problem”¹ (page 271). Different decision analysis approaches exist which could be broadly divided into qualitative and quantitative types; all approaches contain the definition of Objectives and Criteria, identification of Alternatives and Options, collection of Data and Evidence, and elicitation of Consequences and Preferences. However quantitative approaches move beyond this to quantify values (or utilities), trade-offs and uncertainty, and aggregate all components together using a model, i.e. algorithm, which can be as simple as a weighted average. Extension of decision analysis applications to include decisions problems with multiple objectives led to the foundations of multiple criteria decision analysis (MCDA) by Keeney and Raiffa², effectively a fully quantitative decision analysis approach.

Evidence on whether or not the use of an algorithm is a necessary step for the aggregation of values, trade-offs and uncertainty (e.g. as part of MCDA), or whether it can be left to decision-makers’ own capabilities exist from the cognitive psychology literature since the 1950s. Initially, Meehl illustrated that simple, weighted average models consistently outperformed clinical predictions of behavior³, with Miller shortly after indicating that a human brain can at one time keep five to nine pieces of information⁴. In the last decade, Kahneman acknowledged that the human integrator has limited capacity (or human brain lacks such an “integrator” altogether)⁵, with Montibeller and Winterfeldt more recently describing the effects of focusing on a limited number of effects due to limited mental capacity as “myopic problem representation”⁶.

Response to the ICER value framework

Regrettably, although we are not aware of the type of MCDA method(s) considered and tested by ICER together with its independent committees for weighting individual elements, dismissing these methods altogether on the ground that they are not “robust enough to add to reliability of value judgements” (pages 19-20 of the ICER value framework update document) sounds like ignoring many successful applications of these methods across a number of areas, including in drug evaluation⁷⁻¹³ and other non-health application contexts¹⁴⁻¹⁸, if not ignoring Decision Analysis as a whole application field. This is not to say that the application of MCDA in drug evaluation or HTA comes with no challenges or limitations

¹⁹⁻²¹, but dismissing these prematurely will leave no opportunity whatsoever for their appropriate development and effective application.

Unavoidably, whether or not these methods are judged to be “too complicated for reliable use” (page 20 of the ICER value framework update document) or not, will depend on the knowledge, expertise and experience of the people facilitating the overall process, especially during the stage of building a model of values by eliciting value preferences and their trade-offs. In terms of the “complication” claim, for building a fully quantitative MCDA model of five different drugs with the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use, 4-6 experts were involved within a timeframe of six hours ²². In terms of the “reliability” claim, three separate studies modelling the harms of drugs with different groups of experts produced similar results with high inter correlations proving a high degree of reliability and accuracy ²³. Another early HTA study with two rounds of preferences elicitation with different participants across three different countries resulted in virtually identical results (authors’ own work, under review). In any case, for some relatively easier decision problems the use of qualitative decision analysis methods (or other methods) might be adequate. Conditions for the choice of quantitative approaches over qualitative ones could be based on the decision’s importance and analysis complexity, as for example the severity of the disease indication, the unmet clinical need, the number of outcomes being assessed, the type of trade-offs to be valued and the performance of the treatments.

Similarly, in response to any concerns “that there are no validated or consensus methods to integrate these factors into overall judgements of value”, quantitative decision analysis methods are the most validated methods for carrying out such integration of partial components of value judgements for deriving an overall function of value, as evident through the many theoretical and empirical applications in Keeney’s landmark book, *Value Focused Thinking* ²⁴, which explains how the overall value of an option is derived based on the extent to which an objective or number of objectives are judged to add value, and the elicitation of trade-offs that provide a common measure of added value. The implication for any drug evaluation, including HTA, is that although clinical evidence on drug performance for efficacy, safety and quality are based on objective evidence, subjective judgements are always needed for a number of context and evidence related concerns, as for example the appropriateness of the data for the intended disease indication, the clinical meaningfulness of the data, or the relative clinical relevance of different benefits and risks. It is in regards to this subjective interpretation of objective data that the use of quantitative decision analysis methods can be of great worth, as they can accommodate these aspects in a structured and transparent way instead of leaving them to become randomly incorporated through ad hoc and vague efforts.

Furthermore, albeit the establishment of cost-effectiveness thresholds, and therefore any “value-based prices”, are associated with a number of theoretical and practical challenges if not limitations^{25,26}, we are glad to see that one of the ultimate aims of ICER is to “engage all stakeholders in a shared process of learning” in order to “offer a transparent, reliable approach” for integration of benefits (page 23 of the ICER value framework update document). In this regard, the social psychology literature could be very insightful. In terms of learning processes, it should become clear that preferences do not just “sit in our heads” waiting to be extracted but they need to become constructed in a process of value measurement as part of which “added value” is always a matter of judgement. Construction of preferences can be facilitated through group elicitation processes and it could be argued that “many heads are better than one”, as it has been illustrated through an experiment on probability distributions obtained from individual versus group-consensus²⁷. Because of a number of problems relating to interaction processes and cognitive processing, interacting groups (process techniques) might fail to generate judgements as accurate as those of their most capable members, but a combination of group facilitation with judgement analysis and information technology can significantly improve the performance of group’s interaction²⁸.

Recommendations on the use of quantitative decision analysis and decision conferencing

Among the most important features of quantitative decision analysis approaches and MCDA is the encompassing integration of all relevant benefits for a decision problem, and their value trade-offs, into an overall value function. The ICER value framework adopts a clear conceptual structure with a well-defined set of benefits. An incremental cost utility ratio (i.e. incremental cost per QALY gained) acts as the key evaluation metric, with the appraisal committee members asked to vote individually on the existence or not of any other benefits or disadvantages and contextual considerations in a deliberative manner, before being asked to reflect on the voting results as part of the final voting on interventions’ long-term value for money. This last stage of “human integration” lacks transparency but is also prone to fail and susceptible to bias due to limited mental capacity to support such complex tasks, as evident in the behavioral and decision science literature.

Value preferences could be constructed via decision conferencing, defined as “a gathering of key players who wish to resolve important issues facing their organisation, assisted by an impartial facilitator who is expert in decision analysis, using a model of relevant data and judgements created on-the-spot to assist the group in thinking more clearly about the issues”²⁵ (page 54). Typical stages of decision conference workshops include exploring the issues, structuring and building the model, exploring the model and agreeing on the way forward, all of which can be in alignment with requisite modeling: a decision model whose form and content are sufficient to solve a particular problem²⁹. Among the

requirements for constructive decision conferencing processes are ensuring that a diversity of perspectives are represented and a feeling of “cohesiveness” exists between participants as part of which different opinions are being heard in a trusted manner; group numbers of between 7 and 15 participants have shown to be ideal as they are small enough to allow participants to reach an agreement but sufficiently large to represent all perspectives and interests ³⁰, which together with appropriate facilitation can lead to effective outputs from the group. Hundreds of successful decision analysis applications, world-wide, exist for which preferences have been constructed using decision conferencing ^{31,32}.

Assuming agreement has been reached in terms of the level of cost-effectiveness threshold(s), adjusting the threshold or the interventions’ incremental cost utility ratio in order to accommodate for other benefits and contextual considerations should be a possible task. For example, a “baseline” threshold could be expanded proportionally with any additional value (of other benefits and contextual considerations) not captured by the QALY component ³³. Alternatively, assuming the existence of a well-defined budget for allocation of resources within a particular indication or therapeutic area, a value function could be used together with the purchasing costs of the interventions to calculate multi-dimensional value for money ratios. This would point towards the use of multi-criteria portfolio decision analysis, aiming to maximize benefits given a budget constraint, while allowing for opportunity costs to be naturally incorporated ³⁴. In any case, further research would be unavoidably required to develop and test such new methodological applications.

Conclusion and our commitment

Overall, we believe that the combination of quantitative decision analysis together with decision conferencing should be considered more seriously by ICER for the purpose of integrating together the various benefit components of interventions through the engagement of different stakeholders following group processes for the construction of value preferences. In case there is interest in any of the above, we would be happy to explore establishing some form of collaboration between LSE and ICER, as for example by conducting case study work that involves quantitative decision analysis and the organization of decision conferencing to arrive the value of an intervention.

References

1. Raiffa H. *Decision analysis: Introductory Lectures on choices under uncertainty*. Addison-Wesley; 1968.
2. Keeney R, Raiffa H. *Decisions with multiple objectives: preferences and value trade-offs*. 1993 ed. Cambridge: Cambridge University Press; 1976.
3. Meehl PE. *Clinical versus statistical prediction : a theoretical analysis and a review of the evidence*. Minneapolis: Minneapolis : University of Minnesota Press; 1954.
4. Miller GA. The magical number seven, plus or minus two: some limits on our capacity for processing information. *Psychological Review*. 1956;63(2):81-97.
5. Kahneman D. *Thinking, fast and slow*. London : Allen Lane ; Penguin; 2011.
6. Montibeller G, Winterfeldt D. Cognitive and Motivational Biases in Decision and Risk Analysis. *Risk Analysis: An International Journal*. 2015;35(7):1230-1251.
7. Nutt DJ, King LA, Phillips LD. Drug harms in the UK: a multicriteria decision analysis. *The Lancet*. 2010;376(9752):1558-1565.
8. Angelis A, Montibeller G, Hochhauser D, Kanavos P. Multiple criteria decision analysis in the context of health technology assessment: a simulation exercise on metastatic colorectal cancer with multiple stakeholders in the English setting. *BMC Medical Informatics and Decision Making*. 2017;17(149).
9. Felli JC, Noel RA, Cavazzoni PA. A multiattribute model for evaluating the benefit-risk profiles of treatment alternatives. *Medical Decision Making: An International Journal Of The Society For Medical Decision Making*. 2009;29(1):104-115.
10. Marsh K, Zaiser E, Orfanos P, et al. Evaluation of COPD Treatments: A Multicriteria Decision Analysis of Aclidinium and Tiotropium in the United States. *Value in Health*. 2017;20(1):132-140.
11. Moore A, Crossley A, Ng B, Phillips LD, Sancak Ö, Rainsford KD. Use of multicriteria decision analysis for assessing the benefit and risk of over-the-counter analgesics. *The Journal of Pharmacy and Pharmacology*. 2017;69(10).
12. Nixon R. A case study using the PrOACT-URL and BRAT frameworks for structured benefit risk assessment. *Biometrical Journal Biometrische Zeitschrift*. 2016;58(1):8.
13. Angelis A. Evaluating the benefits of new drugs in health technology assessment using multiple criteria decision analysis: a case study on metastatic prostate cancer with the dental and pharmaceuticals benefits agency (TLV) in Sweden. *MDM Policy & Practice*. 2018;3(2).
14. Keeney RL, von Winterfeldt D. Managing Nuclear Waste from Power Plants. *Risk Analysis*. 1994;14(1):107-130.
15. Phillips LD. The Royal Navy's Type 45 story: a case study. In: Salo A, Keisler J, Morton A, eds. *Portfolio Decision Analysis: Improved Methods for Resource Allocation*. New York: Springer-Verlag; 2011:53-75.
16. Gregory R. Using Stakeholder Values to Make Smarter Environmental Decisions. *Environment: Science and Policy for Sustainable Development*. 2000;42(5):34-44.
17. Bana e Costa CA, Antão da Silva P, Nunes Correia F. Multicriteria evaluation of flood control measures: the case of Ribeira do Livramento. *Water Resources Management*. 2003;18:263-283.
18. French S, Kelly N, Morrey M. Decision conferencing and the international chernobyl project. *Journal of Radiological Protection*. 1992;12(1):17-28.
19. Phillips LD. Benefit-risk modeling of medicinal products: Methods and applications. In: Sashegyi A, Felli J, Noel R, eds. *Benefit-Risk Assessment in Pharmaceutical Research and Development*. Boca Raton, FL: CRC Press; 2014.
20. Morton A. Treacle and Smallpox: Two Tests for Multicriteria Decision Analysis Models in Health Technology Assessment. *Value in Health*. 2017;20(3):512-515.
21. Marsh K, Sculpher M, Caro JJ, Tervonen T. The Use of MCDA in HTA: Great Potential, but More Effort Needed. *Value in Health*. 2018.
22. EMA. Benefit-risk methodology project. Work package 3 report: Field tests. 2011;EMA/227124/2011:29. Accessed 26 July 2016.

23. van Amsterdam J, Nutt D, Phillips L, van Den Brink W. European rating of drug harms. 2015;29(6):655-660.
24. Keeney R. *Value focused thinking: a path to creative decision making*. Cambridge: Harvard University Press; 1992.
25. Phillips LD, Bana e Costa CA. Transparent prioritisation, budgeting and resource allocation with multi-criteria decision analysis and decision conferencing. *Annals of Operations Research*. 2007;154(1):51-68.
26. Claxton K, Martin S, Soares M, et al. Methods for the estimation of the National Institute for Health and care excellence cost- effectiveness threshold. *Health Technology Assessment*. 2015;19(14):1-503.
27. Phillips LD. *Group elicitation of probability distributions: are many heads better than one?* : Kluwer Academic Publishers; 1999.
28. Reagan-Cirincione P. Improving the Accuracy of Group Judgment: A Process Intervention Combining Group Facilitation, Social Judgment Analysis, and Information Technology. *Organizational Behavior and Human Decision Processes*. 1994;58(2):246-270.
29. Phillips L. A theory of requisite decision models. *Acta Psychologica*. 1984;56:29-48.
30. Phillips L, Phillips M. Faciliated Work Groups: Theory and Practice. *The Journal of the Operational Research Society*. 1993;44(6).
31. Dodgson J, Spackman M, Pearman A, Phillips L. Multi-Criteria Analysis: A Manual. In. 2009 ed. London: Department for Communities and Local Government; 2000.
32. Phillips L. Decision Conferencing. In: Edwards W, Miles R, von Winterfeldt D, eds. *Advances in Decision Analysis: From Foundations to Applications*. Cambridge: Cambridge University Press; 2007.
33. Phelps C, Madhavan G. Resource allocation in decision support frameworks. *Cost Effectiveness and Resource Allocation*. 2018;16(S1).
34. Salo A, Keisler J, Morton A. *Portfolio decision analysis : improved methods for resource allocation*. New York ; London: New York ; London : Springer; 2011.



June 10, 2019

Steven, D. Pearson, MD MSc, FRCP
President, Institute for Clinical and Economic Review
Boston, MA 02109

Dear Dr. Pearson,

On behalf of LUNGevity Foundation, the nation's preeminent lung cancer nonprofit that funds research, provides education and support, and builds communities for the approximately 230,000 Americans diagnosed with lung cancer each year and the 538,243 Americans living with the disease,¹ we appreciate the opportunity to submit our comments in response to the request for comments on ICER's 2020 Value Assessment Framework. We applaud ICER for providing stakeholders this opportunity to submit feedback prior to the release of the draft Value Assessment Framework and we encourage ICER to review all comments and reach out to stakeholders for more in-depth discussions of the comments prior to drafting the draft Value Assessment Framework.

LUNGevity's mission is to improve outcomes for people diagnosed with lung cancer. Our goals are three-fold: (1) to accelerate research to patients that are meaningful to them; (2) to empower patients to be active participants in their care and care decisions; and (3) to help remove barriers to access to high quality care. We have the largest lung cancer survivor network in the country and actively engage with them to identify, understand and address unmet patient needs. We also have a world class [Scientific Advisory Board](#) that guides the programs and initiatives of the organization and contributes to public comment letters such as this one.

In this era of unprecedented scientific advancements for the treatment of lung cancer, particularly personalized medicine and immunotherapy, we recognize the importance of balancing innovation with higher costs of medicines while ensuring that patients have access to life-saving therapies. We appreciate the work and the desire to create tools to facilitate the conversation between healthcare providers and patients around treatment options. We also recognize the incredible responsibility of ensuring that ALL stakeholders – *especially patients* – are fully represented in developing these tools and the utmost importance of including robust data that represents how the therapies are used in practice.

In summary, we recommend the following to make the ICER model more rigorous and patient-centric:

1. Incorporation of methodological and end-user transparency
2. Inclusion of patient experience and clinical practice perspective
3. Use of patient experience metrics that are not aggregate and capture the true meaningful benefit of a treatment approach, across the disease continuum of care
4. Integration of real-world evidence and real-world data into the ICER value assessment framework

These are discussed in greater detail below.

1. Incorporating both methodological and end-user transparency into the ICER model will make it more acceptable and robust.

Methodological transparency: We understand and appreciate the effort ICER has put in toward building a robust cost-effectiveness model and respect the proprietary nature of the effort; however, the lack of transparency calls into question its validity. Oncology value frameworks such as the ASCO Value Framework² and Memorial Sloan Kettering Drug Abacus³ have made their methodology transparent, and we would encourage ICER to do the same.

Given the rapid evolution of lung cancer therapies (there were seven new FDA approvals for lung cancer in 2015⁴), we encourage ICER to be fully transparent about the selection process of the drugs being evaluated (why are drugs that have not even been approved yet being included in the model?), the expert clinicians who are advising on the real-world use of the therapies, the model inputs and how the model will be used. At a minimum, we encourage that the models be peer reviewed by disease state experts.

End-user transparency: ICER has maintained that the models developed are end-user-neutral and will not be used to make reimbursement or payment decisions. However, according to the Federal Register / Vol. 81, No. 48 / Friday, March 11, 2016 /Proposed Rules, Medicare payment model under section 1115A of the Social Security Act (the Act), CMS states, “We propose to use indications-based pricing where appropriately supported by published studies and reviews or evidenced-based clinical practice guidelines, such as the ICER reports, to more closely align drug payment with outcomes for a particular clinical indication.” While this proposed model did not move forward, CMS’ interest in using ICER reports causes much concern.

We recommend that ICER recognize the impact of their models and ensure that they are created in a robust, evidence-based and patient-centric manner and recognize how their model may be used in clinical practice as well as to make reimbursement decisions.

2. Including the patient experience will be invaluable in determining the true value of a treatment approach.

With progress in lung cancer treatment, survivors are living longer. It is imperative to incorporate the survivor perspective rather than make generalized statements about all people with lung cancer as the patient/survivor populations can be very different. Contrary to popular belief, lung cancer is becoming a disease of the young and the non-smoker.⁵ A young, 30-year-old, stage IV survivor may value benefits from a treatment regimen very differently than a 70-year-old survivor. These nuances would be captured through **patient preference** studies and quality of life metrics which are often not included in existing clinical trial data.

LUNgevity Foundation has spearheaded the first lung cancer advocacy-driven patient preference initiative. The initiative, *Project Transform*, is a multi-year, multi-stakeholder collaborative endeavor between LUNgevity and Ohio State University. It encompasses core principles of patient-centered outcomes research (PCOR), in line with LUNgevity’s mission of providing a voice to the lung cancer

patient. The goal of *Project Transform* is to change the paradigm in lung cancer from assumptions being made about patients' wishes to evidence-based conclusions about patients' need and desires. Currently in its third year of a nationwide patient preferences survey, the project built its quantitative phase through a rigorous patient engagement model in which lung cancer patients provided direct feedback and input on the project implementation.^{6,7} An important finding from the quantitative component showed that patients who had received 2 or more lines of therapies had different preferences than those patients who were on their first treatment. Specifically, patients who had been on more than one line of therapy were willing to give up only 2.2 health month equivalents (additional months of progression-free survival a new treatment would need to provide for participants to accept additional side effects) for a drug that caused increased long-term side effects, as compared to 3.7 months by patients on their first treatment.⁸ These results demonstrate that patient experience is very heterogeneous and hence, should be taken into account in value assessment frameworks.

The need for capturing patient experience in value frameworks will become even more important as the concept of “comparative tolerability” enters the lung cancer space. A recent study of three PARP inhibitors in high-grade ovarian cancer demonstrated that while all three provided equivalent survival benefits, one of the inhibitors had a significantly lower toxicity profile than the other two. While the study was not designed to be a head-to-head comparison among the three drugs, it highlights the importance of quality-of-life measures (gathered through patient preference studies) in such situations where primary endpoints such as overall survival are met and may not differ dramatically across different therapies.⁹ In such situations, patient preference data will be of paramount importance in determining appropriate care for a patient, where standard-of-care may evolve or multiple options exist.

3. Use of aggregate metrics such as QALYs and evLYGs do not capture patient-level data especially in an era of precision medicine.

The lung cancer treatment landscape has rapidly evolved over the past five years, with the Agency approving more than 15 new treatments for advanced-stage non-small cell lung cancer (NSCLC) — more than in the prior 15 years combined. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, diagnosed in about 85% of people with lung cancer.^{10,11} The complex nature of this disease requires personalized management plans for patients.¹¹ Since the discovery of the first epidermal growth factor receptor (EGFR) mutation in lung cancer in 2004, targeted therapies have become a major component of the treatment arsenal of NSCLC patients.¹²⁻¹⁴ Now more than 20 driver mutations in adenocarcinoma have been identified — EGFR, ALK, ROS, RET, ERB2/HER2 mutations, ERB2/HER2 amplifications, MET amplifications, MET mutations, TRK, BRAF, KRAS.^{15,16} In concert with the identification of an increasing number of targetable mutations is the development of novel, potent, and more specific targeted therapies. For example, the first-line treatment options for EGFR and ALK positive lung cancer has changed in the last year. Furthermore, even for those NSCLC patients without a driver mutation, first-line immunotherapy with or without chemotherapy has become the standard of care.^{17,18} This rapid evolution of care has increased the need to re-think patient preferences. Lung cancer patients are now living longer, higher quality lives.

QALYs or quality-adjusted life-years have long been used by economists to forecast healthcare financial decisions. While the QALY is easy to use, in their *New England Journal of Medicine*,

Neumann and colleagues point out that the QALY value typically used by healthcare economists in fact underestimates the impact of a drug.¹⁹ In addition, QALYs are not appropriate for measuring complex health interventions (such as lung cancer treatment) where “gain of health” is not the only measure.²⁰ Also, QALY is an aggregate metric—it does not capture patient-level data in making economic predictions. An ideal model is one that includes patient-level metrics that can customize a prediction to an individual patient, in line with the tenets of precision medicine.

Furthermore, unlike other diseases where QALYs may have some applicability, lung cancer is not a singular disease. Rather, it is a continuum where stage of diagnosis, presence or absence of actionable mutations, recurrence, and end-of-life care would impact a patient’s decision about a treatment option. Using QALYs may not adequately capture what different patients value along the lung cancer continuum.²¹

In her New York Times blog, ovarian cancer survivor Susan Gubar poignantly captures the inadequacies of QALYs in treatment decisions.²² She writes, “[w]hatever the estimate, a crude ratio of cost effectiveness, like the QALY, seems presumptuous. How can qualitative factors (nausea, fatigue) be converted into quantitative numbers? How can general calculations account for individual variations (my preference for fatigue over nausea) or overriding personal beliefs and principles about what constitutes a valuable existence?”

We commend ICER for developing and utilizing a new metric - Equal Value of Life Years Gained (evLYG) - that evenly measures any gains in length of life, regardless of the treatment’s ability to improve patients’ quality of life. While evLYGs moves the focus of measurement from life extension, it continues to be an aggregate metric.

As an alternative to QALY and evLYGs, patient-reported outcomes and quality of life metrics can be used to accurately capture the differences in patient perspective along the lung cancer continuum. As pointed out by ASCO in their value framework discussion, inclusion of Patient Report Outcomes (PROs) makes their model more robust.² We encourage ICER to consider PROs and Quality of Life metrics, especially given that global lung cancer therapy trials now incorporate PRO measurement as a part of their study design.

4. There is immense value in incorporating real-world data and real-world evidence about clinical practice.

We encourage ICER to assess evidence once a drug has been used in practice for a significant amount of time to accurately capture the impact a drug has made on the survivor community. This is also related to our previous comments on PRO use in clinical trials. To be comprehensive, we recommend ICER to incorporate real-world patient experience and clinical practice data for the following reasons, given that PRO data collection is relegated to clinical trials.

1. Despite an expansion of clinical trials in global sites, an overwhelming proportion of trial participants are Caucasian (86% in 2014 vs. 92% in 1997).²³ Conducting a patient preference study within a clinical trial setting, while beneficial for submission purposes, is a missed opportunity for truly capturing the patient experience in a real-world setting, as the participant



composition does not reflect the true prevalence of the disease in a real-world setting in different racial and ethnic communities.²⁴

2. Furthermore, lung cancer clinical trials often exclude patients with brain metastases and low performance status.²⁵ Given that a majority of advanced-stage patients present with brain metastasis at the time of diagnosis or are very sick due to the high symptom burden of lung cancer, conducting patient experience studies within a pristine clinical trial cohort does not capture the lived experience of a lung cancer patient outside of a trial setting.

As real-world data traditionally comes from four sources (clinical data from electronic health records, administrative/claims data, patient-generated/reported data, and third-party data sources through cross-industry data collaborations such as Project Data Sphere), we see ICER as being in an excellent position to develop evidentiary standards for using real-world data in value frameworks.

Conclusion

LUNGeVity sincerely thanks you for the opportunity to comment on ICER's Value Assessment Framework. We look forward to additional opportunities to contribute to ICER's ongoing work and encourage the Institute to provide more opportunities for stakeholder input into its process for developing and refining its value assessment framework.

As stated, the areas of concern that we have outlined above can be actively discussed with my staff, myself, and LUNGeVity's Scientific Advisory Board, which is made up of some of the world's leading experts in lung cancer biology, practice management, access to innovative medicines, and overall patient care. I encourage you and ICER to access our expertise.

I can be reached at 240-454-3100 or aeferri@lungevity.org if you have any questions or would like to engage in further dialog.

Thank you for your attention to this very important matter.

Sincerely,

A handwritten signature in dark ink, appearing to read "Andrea Stern Ferris", written in a cursive style.

Andrea Stern Ferris
President and Chairman
LUNGeVity Foundation

REFERENCES:

1. SEER. Cancer Stat Facts: Lung and Bronchus Cancer. 2019; <https://seer.cancer.gov/statfacts/html/lungb.html>. Accessed June 9, 2019.
2. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Aug 20 2016;34(24):2925-2934.
3. Villaruz LC, Socinski MA. The clinical viewpoint: definitions, limitations of RECIST, practical considerations of measurement. *Clinical cancer research : an official journal of the American Association for Cancer Research*. May 15 2013;19(10):2629-2636.
4. Waqar SN, Bonomi PD, Govindan R, et al. Clinician Perspectives on Current Issues in Lung Cancer Drug Development. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. Sep 2016;11(9):1387-1396.
5. Pelosof L. CA, L. Horn, A. Madrigales, J. Cox, J.N. Roberts, J. Minna, J. Schiller. Increasing Incidence of Never Smokers in Non Small Cell Lung Cancer (NSCLC) Patients. Paper presented at: World Conference on Lung Cancer 2015.
6. Bridges JFP, Janssen EM, Ferris A, Dy SM. Project Transform: engaging patient advocates to share their perspectives on improving research, treatment and policy. *Current medical research and opinion*. Mar 9 2018:1-8.
7. Dy SM, Janssen EM, Ferris A, Bridges JF. Live, Learn, Pass It on: A Patient Advocacy Engagement Project on the Lived Experience of Lung Cancer Survivors. *Journal of patient experience*. Dec 2017;4(4):162-168.
8. Ferris A, Bridges JFP, Jansse E, Basu Roy U. Line of Therapy and Patient Preferences Treating Lung Cancer: A Discrete-Choice Experiment. Paper presented at: 2018 World Conference on Lung Cancer 2018; Toronto, CA.
9. Sackeyfio A, Nussey F, Friedlander M, Pujade-Lauraine E. Comparative efficacy and tolerability of the PARP inhibitors, olaparib 300 mg tablets BID, niraparib 300 mg capsules QD and rucaparib 600 mg tablets BID as maintenance treatment in BRCA-mutated (BRCAm) platinum-sensitive relapsed ovarian. Paper presented at: 2018 SGO Annual Meeting 2018; New Orleans.
10. Thomas A, Liu SV, Subramaniam DS, Giaccone G. Refining the treatment of NSCLC according to histological and molecular subtypes. *Nature reviews. Clinical oncology*. Sep 2015;12(9):511-526.
11. Johnson DH, Schiller JH, Bunn PA, Jr. Recent clinical advances in lung cancer management. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 1 2014;32(10):973-982.
12. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *The New England journal of medicine*. May 20 2004;350(21):2129-2139.
13. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. Jun 4 2004;304(5676):1497-1500.
14. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib.

- Proceedings of the National Academy of Sciences of the United States of America*. Sep 7 2004;101(36):13306-13311.
15. Hirsch FR, Suda K, Wiens J, Bunn PA, Jr. New and emerging targeted treatments in advanced non-small-cell lung cancer. *Lancet*. Sep 3 2016;388(10048):1012-1024.
 16. Soo RA, Stone EC, Cummings KM, et al. Scientific Advances in Thoracic Oncology 2016. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. May 27 2017.
 17. NCCN. NCCN Guidelines for Patients® Non-Small Cell Lung Cancer. 2017; <https://NCCN.org/patients/guidelines/content/PDF/nscl.pdf>. Accessed July 18, 2018.
 18. NCCN. NCCN Guidelines for NSCLC Version 4.2019.; https://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf. Accessed June 9, 2019.
 19. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the \$50,000-per-QALY threshold. *The New England journal of medicine*. Aug 28 2014;371(9):796-797.
 20. Payne K, McAllister M, Davies LM. Valuing the economic benefits of complex interventions: when maximising health is not sufficient. *Health economics*. Mar 2013;22(3):258-271.
 21. Garau M, Shah KK, Mason AR, Wang Q, Towse A, Drummond MF. Using QALYs in cancer: a review of the methodological limitations. *Pharmacoeconomics*. Aug 2011;29(8):673-685.
 22. Gubar S. Pricing a Year of Life. *The New York Times* 2016.
 23. Knepper TC, McLeod HL. When will clinical trials finally reflect diversity? 2018; <https://www.nature.com/articles/d41586-018-05049-5#ref-CR1>. Accessed 2019, June 4.
 24. Ramamoorthy A, Pacanowski MA, Bull J, Zhang L. Racial/ethnic differences in drug disposition and response: review of recently approved drugs. *Clinical pharmacology and therapeutics*. Mar 2015;97(3):263-273.
 25. Bonomi P, Blumenthal G, Ferris AS, et al. Making Lung Cancer Clinical Trials More Inclusive: Recommendations for Expanding Eligibility Criteria. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. Jun 2018;13(6):748-751.

June 10, 2019



Steven D. Pearson, M.D., M.Sc. FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th Fl.
Boston, MA 02109

main: 617 • 674 • 5100 fax: 617 • 674 • 5101

Massachusetts Biotechnology Council
300 Technology Square, Eighth Floor
Cambridge, MA 02139

Re: 2020 Value Assessment Framework Improvements

Dear Dr. Pearson,

MassBio appreciates this opportunity to comment on the Institute for Clinical and Economic Review (ICER) current Value Assessment Framework (the “Framework”) and how it can be improved to properly measure the value that prescription drugs bring to patients and the healthcare system. Value assessments must be done accurately and thoroughly to ensure patients have access to breakthrough therapies and cures. MassBio represents more than 1,200 life sciences companies, academic institutions, service providers and patient organizations, the majority of which are directly engaged in the research, development and manufacturing of innovative products that solve unmet medical needs for patients around the world. MassBio is committed to advancing Massachusetts' leadership in the life sciences to add value to the healthcare system and improve patient lives.

MassBio is an active stakeholder both in Massachusetts and nationally in the debate over the value of prescription drugs. This is not an effort to protect the status quo, but rather to be part of developing real solutions that protect patient access and reward innovation. In fact, between the increased political attention to drug pricing and the wave of new, complex and life-saving therapies and cures coming to market, our involvement is necessary and critical.

While we understand the need for cost-effectiveness research, we believe that ICER's conclusions on a drug's cost-effectiveness are based on limited data and have an outsized impact on the marketplace, leaving no room for debate, uncertainty, or ambiguity.

Cost-effectiveness calculations are inherently black or white. However, we know that assessing a drug's value based on a snapshot in time based on what data is currently available, does not provide the healthcare marketplace with a full picture of the current or future benefit of the drug to a patient, the healthcare system, or society. Yet, despite the obvious limitations to the report, payers, policymakers, and others are taking ICER's reports as gospel.

As ICER updates its Value Assessment Framework for 2020 and beyond, MassBio would recommend the following improvements to the Framework and how ICER operates more broadly:

1. ICER should not rush to release public conclusions based on incomplete data

Many of ICER's analysis are released before a drug is even approved by the FDA and most of ICER's reports are based on very limited data sets. This is a serious disservice to patients and the healthcare system. As we've recently seen, ICER's conclusions on a drug released pre-FDA approval are made immediately inaccurate post-FDA approval because a drug's label was more expansive than expected. Similarly, when ICER rushes to release a report on a new drug based only on clinical trial data, they are assuming real-world use and performance of that therapy will mirror trial results. In this hurry to issue conclusions, ICER is directly impacting patient access to breakthrough therapies.

While we know ICER is simply working with what's available, we would argue: "what's the rush?" A more accurate ICER review that includes real-world evidence, even if it's 2-4 years post-approval, will deliver much greater value to the healthcare system compared to any potential incremental gain from using an ICER review only based on clinical trial data.

2. When available, ICER should incorporate real-world evidence when assessing if a new therapy provides additional value over existing standards of care at the patient level

In cases where ICER is assessing a new therapy's effectiveness and value to patients versus the existing standards of care, there is regularly ample real-world evidence that would provide significant context about how the new therapy would act in the real world on a patient-by-patient basis. ICER must consider data from electronic health records (EHRs), social media, care management data, and other sources to understand the current standards of care, how patients are responding, and how mitigating factors such as adherence and insurance design are impacting patient outcomes.

Such data can show trends such as patients being worse off than ICER's standard model estimates (e.g. in more pain), or that patients are failing more widely than expected on existing treatments, or even identify broader patient populations that would benefit from the new therapy than ICER's model estimates. In addition, real-world data is likely to show that patient populations are experiencing comorbidities at a much higher rate than expected which can have a significant impact on the value a new therapy can offer on a patient level basis. Further, EHRs and the like will show that patients may be taking numerous other prescriptions that may affect outcomes.

Lastly, ICER's current methodology supports and helps ingrain the existing "fail first" insurance design by including assumptions in their comparative data that patients have already, or need to, fail on existing standards of care before they will try a new therapy. This is despite ample data in numerous disease states showing that patients have already failed on numerous or all existing therapies, sometimes in short periods of time.

In summary, ICER's model assumes that existing therapies will work for a broad patient population where real-world data may show otherwise. ICER's model may also underestimate a patient's need or desire to switch to a new therapy right away. For all the reasons listed above, ICER must consider real-world evidence in their model to consider patient-level outcomes for their overall value conclusions.

3. ICER's model should not set an arbitrary cap on drug spending and should make clear their affordability analysis is an opinion with no context to specific circumstances

As an overall threshold matter, we do not support calculating short-term budget impacts as bearing any meaningful connection to a particular therapy's overall cost effectiveness or true value to patients or the healthcare system, even if such an impact could reliably be determined based on available data. This is because estimating the short-term impact of a particular therapy on public budgets and payer profits is

entirely unrelated to its comparative clinical effectiveness over prior treatments on either a population-wide or a patient-by-patient basis.

Further, ICER's reliance on the wholesale acquisition cost (WAC) to calculate short-term budgetary impacts risks greatly overstating true costs. Unfortunately, this in turn risks overreactions by payers and policymakers in connection with the perceived cost impact of new drugs. As you know, WAC pricing does not incorporate rebates, discounts, and other price concessions that are commonly applied to drug purchases in the commercial market and is in fact required in connection with certain federal health care programs. We understand that in many cases the precise amount of a rebate or discount is protected, confidential information. That said, and particularly given the generalities utilized in other aspects of the Framework, the unavailability of the precise data should not deter ICER from arriving at more reliable spend figures through rebate estimates.

Payers are the ultimate determiner of whether a new therapy offers value to their covered lives. However, ICER's determinations of whether spending on a new therapy is appropriate or not is viewed by the public, policymakers, and others as the final say of whether a drug is "too expensive" or not for the healthcare system. Such judgements cannot be made by ICER based on an arbitrary affordability threshold they set. Payers, based on their specific considerations of budget constraints, preferences, and tradeoffs should be making budget impact decisions on their own. Indeed, as payers will admit, an increase in prescription drug spending is not necessarily a bad thing if it provides improved health outcomes and lowers spending in other areas.

Again, by issuing a proclamation about budget impact with no regard to specific circumstances, ICER threatens patient access to breakthrough therapies by steering payers' decision making based on incomplete and potentially inaccurate data.

4. ICER must publicly explain if, or how, they include any qualitative information they receive such as patient input into their modeling and final analysis

Transparency around ICER's modeling does not include any indication for how it incorporates qualitative data or information gathered from 3rd party stakeholders during public hearings or comment periods. This information, often from patients directly impacted by the disease, or groups representing those patients, offers valuable insight about the current standard of care for their condition, their existing costs, their quality of life, and the potential to improve all these areas with a new therapy. Patients are the ultimate consumer of new therapies and their perspective is as important, if not more, than any other in the healthcare system.

Again, on behalf our members, we thank you for this opportunity to comment on certain aspects of the Framework. We look forward to continuing these discussions going forward. Please do not hesitate to contact me if you have any questions about any of the comments above.

Sincerely,

A handwritten signature in black ink, reading "RK Coughlin". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

Robert K. Coughlin
President & CEO

May 24, 2019

Institute for Clinical and Economic Review (ICER)
Two Liberty Square
Ninth Floor
Boston, MA 02109

Dear ICER Value Assessment Framework Review Team:

Mental Health America (MHA), the Depression Bipolar Support Alliance (DBSA), and the National Alliance on Mental Illness (NAMI) thank the Institute for Clinical and Economic Review (ICER) for inviting public comment on the update of the Value Assessment Framework for 2020 and beyond. The undersigned urge ICER to build a microsimulation of the relationship between improved behavioral health outcomes and future loss of eligibility for means-tested public programs (e.g. Medicaid, disability Medicare and income, Section 8 housing) due to increased earnings (or projected earnings based on increased educational attainment for children) from reduced behavioral health challenges.

Federal and state governments are the largest payers of behavioral health care in the United States. Governments only provide health care coverage and other safety net programming when individuals reach certain thresholds of income or disability. Thus, public health care payer cost-effectiveness works differently than commercial payer cost-effectiveness. When a public payer invests in effective behavioral health care for an individual, the individual may be more able to work and increase their earnings. If the increased earnings causes the individual to cross above the thresholds of income or disability, the individual will no longer be eligible for public health care coverage and other programming, and be able to seek commercial coverage instead. From the perspective of the public payer, the cost-effectiveness of behavioral health care is not just driven by decreases in later health care utilization related to better behavioral health outcomes, but also by the possibility of not having to pay for any further health care services or other programming as the individual transitions to commercial coverage. Meaningful investments in behavioral health care can be uniquely cost-effective for public payers, and modeling should reflect this.

Note that this scenario is different than modeling increases in productivity and taking a societal perspective on benefit. The approach here continues to take a narrow payer perspective on benefit, but recognizes that public payers have different costs and benefits than commercial insurers. Improvements in the ICER value assessment related to productivity increases would not address the issue raised here.

Modeling public payers is important not only to ensure descriptive accuracy, but also to advance an important normative goal – that the government invest in the long-term functioning of its citizens. By making the analysis described here common practice, ICER can shift the paradigm for how CMS and state Medicaid agencies view costs and benefits – away from trimming health care costs and toward making critical investments that alleviate poverty and disability. Rather than having to model these impacts on an ad-hoc basis during each review in behavioral health,

the undersigned advocate that ICER build a microsimulation for the relationship between behavioral health outcomes and future loss of eligibility for means-tested public programs due to increased earnings, which can be applied across reviews.

The undersigned thank ICER for its consideration on how to ensure that the Value Assessment for 2020 captures value that matters most to individuals and communities.

Sincerely,

Mental Health America

Depression Bipolar Support Alliance

National Alliance on Mental Illness

June 10, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston MA 02109 USA

Dear Dr. Pearson:

Merck & Co., Inc. appreciates the opportunity to provide comments on the proposed updates to the ICER Value Assessment Framework. We share ICER's interest in ensuring American consumers and patients have access to high value health care. We appreciate the modifications and updates that ICER has considered in the past, and we offer the following comments for your consideration for the next iteration of the value framework:

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

We appreciate ICER's willingness to be innovative with respect to context-dependent cost-effectiveness thresholds. Using a higher cost-effectiveness threshold for treatments of ultra rare conditions is also a positive step forward that may improve patients' access to the treatments and encourage future innovations for managing the conditions.

As ICER previously acknowledged, there has been no general agreement on a single cost-effectiveness threshold in the United States. ICER currently uses a range of \$100,000 to \$150,000 per QALY gained to establish its value-based price benchmarks. However, Braithwaite et al indicated that the willingness-to-pay threshold in the US (in 2003 dollars) was between \$109,000 and \$297,000 per QALY gained¹, which is equivalent to \$151,383-\$412,487 adjusted to 2019. WHO, another commonly cited threshold uses 3 times the gross domestic product per disability adjusted life-year. Based on the projection by International Monetary Fund for 2019, this threshold in the US would be \$194,310. Nanavaty and colleagues (2015) noted that thresholds up to \$200,000 per QALY gained may be acceptable in the US.² Therefore, we suggest that ICER adopt higher cost-effectiveness thresholds to develop its value-based price benchmarks for its future reviews.

2. The approach ICER takes to evaluate the magnitude and certainty of net health benefit demonstrated by the clinical evidence:

The magnitude and certainty of health benefits are two different concepts that stakeholders (payers, clinicians, patients, etc.) may need to consider separately when

¹ https://www.jstor.org/stable/40221668?seq=1#page_scan_tab_contents

² <https://www.journalofclinicalpathways.com/article/use-incremental-cost-effectiveness-ratio-thresholds-health-technology-assessment-decisions>

making decisions regarding innovative technologies. Currently, ICER attempts to use a single rating scheme to capture the two concepts together. The scheme is overly cumbersome, including 9 grades (A, B+, B, C+, C, C-, D, P/I, and I). Conceptually, these grades are not straightforward to interpret. To interpret each grade's meaning, one has to refer back to the ICER rating matrix to figure out where the grade stands on the two domains (i.e., magnitude and certainty of health benefits). More importantly, from a decision maker's perspective, a B+ rating may not necessarily mean "better" than a B rating and, similarly, a C+ rating may not mean better than a C or C- rating. Which grade is "better" may depend on how the decision maker trade the magnitude for the certainty of health benefit. Therefore, we suggest ICER assess and report the magnitude and certainty of health benefits separately in its reviews. This is the approach taken by most of the major evidence assessment groups such as GRADE, AHRQ, Cochrane, and USPSTF.

3. The approach ICER takes to incorporate real-world evidence into review
ICER has been relying heavily on clinical trial data for its reviews, which may underrepresent certain patient populations and subgroups. We appreciate ICER's willingness to enhance use of RWE in its future reviews. ICER should routinely assess whether the existing clinical trial data are representative of the relevant patient population and subgroups for each review and whether RWE need to be incorporated to address the real-world effectiveness (vs. efficacy questions) questions. Some data sources, such as Drug Trial Snapshots that FDA posts online, could be useful for this assessment.

Multiple evidence assessment groups (e.g., Cochrane, GRADE, AHRQ EPCs) have developed methodologies and tools to assess the quality of evidence when both RWE and RCTs are incorporated into the same evidence reviews. We encourage ICER to explore these existing methodologies and tools to broaden the use of RWE in its reviews. In addition, ISPOR and ISPE have developed standards for RWE; these standards could be used to assess the quality of individual studies. We suggest ICER use a systematic approach to routinely incorporate RWE into its future reviews and outlines this approach in its 2020 framework update.

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

As discussed by the authors from CEVR, both QALY and evLYG has some limitations in value assessment of medical innovations (<https://cevr.tuftsmedicalcenter.org/news/2018/will-icers-response-to-attacks-on-the-qaly-quiet-the-critics>). While use of both measurements in ICER reviews would provide more information and flexibility for stakeholders to judge the value of a technology, the two measurements alone do not present a full value picture. Other benefits and contextual considerations that are not captured via CEA should be thoroughly incorporated into the ICER review and price benchmarking process (see comment below).

6. 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:

The benefits and contextual considerations for value judgment that cannot be captured via clinical evidence or through cost-effectiveness modeling are currently used to inform discussions among ICER's three regional CEPACs. However, these benefits and considerations have not been used to modify the price benchmarks generated from ICER's cost-effectiveness analyses. It would be appropriate and fair for ICER to establish a mechanism to allow these important benefits and considerations be quantitatively incorporated into the price benchmarking process. To achieve this goal, ICER shall seek input from all relevant stakeholders including patients, families, care providers, payers, clinical researchers, health economists, and policy makers. Methods such as multiple-criteria decision analysis (MCDA) may be explored as an initial step to lay the methodological foundation.

7. Use of a societal perspective for the base case of CEA:

ICER currently conducts CEA from both health systems and societal perspectives. However, the base case of CEA on which the value-based price benchmark is developed from the health system perspective. Given the diversity of ICER reviews' intended stakeholders (patients, payers, caregivers, policy makers, etc.), it would be more appropriate to use a societal perspective as the base case of CEA. The societal perspective is recommended as a base case by the 1st and 2nd panels on cost-effectiveness in health and Medicine, and is also used by the Advisory Committee on Immunization Practices. This will allow ICER to incorporate into its reviews all benefits that matters for patients and the society, such as the impact of the technology on productivity and caregiver burden. We suggest that ICER use the societal perspective for the base case of CEA in its future reviews. Value-based price benchmarking, related policy discussions and press release should all be based on the societal-perspective CEA to ensure the relevance of these works to the most important stakeholders of ICER reviews (i.e., patients and the society as a whole).

8. One-size-fits-all budget impact analysis:

We are concerned that ICER's one-size-fits-all budget impact analysis does not reflect decision-making of with US payers. Budget impact is a function of the size of the health plan, IDN, or PBM; number of patients; treatment pathways and algorithms; cost structures and discounts; formulary management; and many other organization-specific factors as well as data from randomized controlled trials and comparative effectiveness research. Payers should conduct their own budget impact analysis that are customized to their specific needs and situations. ICER's estimates of national budget impact are not relevant to individual payers. We suggest that ICER remove budget impact analysis from its reviews, focusing solely on clinical, economic, and other value of health innovations.

9. Artificially created national budgetary threshold for each new drug:

ICER currently allocates a national budget of \$991 million per year to any new drug that comes to the market and uses this number as a threshold to judge the “affordability” of the drug. This practice carries several serious flaws. First, the level of new spending should not be split evenly among all new drugs without considering each drug’s clinical and economic value; instead, the spending allocated to each new drug should reflect the level of innovation (i.e., value) it delivers. Second, it is not reasonable to use a single budgetary threshold to judge affordability given the diversity of the US healthcare system. This single budgetary threshold does not reflect the specifics of individual payers or institutions. Third, ICER calculates the budgetary threshold based on a series of assumptions or projections (Figure 3 in the 2017 ICER value framework document). The assumptions (e.g., the health care spending growth rate relative to the GDP growth rate, contribution of drug spending to total health care spending in percentage) only reflects ICER’s perspective, not the stakeholders’ perspectives. The projections (e.g., total annual health care spending, the new drugs coming to market each year) were often inaccurate, as suggested by the past records. We believe that using this biased, artificially generated budgetary threshold as a foundation for judging affordability is more misleading than informing, therefore suggest that ICER abandon this practice in its future reviews.

10. Process for seeking stakeholder input:

We suggest ICER consider modifying the process to be more similar to the one used by CDC’s Advisory Committee on Immunization Practices (ACIP). The ACIP has been established for 30+ years and has a transparent and well-accepted process for evaluation, recommendation and funding of new vaccines (<https://www.cdc.gov/mmwr/volumes/67/wr/mm6745a4.htm>). Manufacturers and academics are invited to present cost-effectiveness models which results in a robust and transparent discussion regarding differences in model structures and assumptions and the impact on model results and interpretation of results. We suggest that ICER include a member of ACIP on its steering committee and establish a process for inclusion of alternative approaches for economic modeling and allow presentation of manufacturer models. In addition, ICER should consider creating more opportunities for patient input throughout the entire review process. Patient groups should be consulted early in the process of model development to ensure their perspectives are incorporated into model assumptions and inputs.

Sincerely,

Megan O’Brien, PhD, MPH
Executive Director
Center for Observational and Real World Evidence



June 10, 2019

Institute for Clinical and Economic Review (ICER)
Two Liberty Square
Ninth Floor
Boston, MA 02109

Submitted electronically to publiccomments@icer-review.org

Re: 2020 Update to ICER's Value Assessment Framework

To whom it may concern,

The Muscular Dystrophy Association (MDA) appreciates this opportunity to provide input to the Institute for Clinical and Economic Review (ICER) on its work to update the Value Assessment Framework, specifically regarding suggestions for improvement on the methods that the Institute uses to communicate with stakeholders in the patient community. As an organization with a mission of transforming the lives of individuals affected by neuromuscular diseases through innovations in science and innovations in care, MDA is committed to funding groundbreaking research; accelerating the development of treatments and cures; promoting early identification, diagnosis and treatment; and improving health outcomes. For more than 65 years, MDA has been on the frontlines of research for amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD), and other neuromuscular diseases.

MDA has also previously provided input to ICER on therapy reviews and believes that this exercise to implement suggestions, especially from patients and patient advocacy organizations, to improve the overall review process is an important undertaking. MDA also appreciates the supplementary publication of "*A Patient's Guide to Open Input*" offered on this topic as it signals ICER's commitment to ensuring that the voices of patients and their advocates are reflected in the incoming input that you receive in this process. Patients are the experts in the diseases that they live with in many ways, and heeding the input of patients and patient advocacy organizations is critical.

Paramount for ICER's consideration, and which goes across the three enumerated aspects of the request for information, is that ICER should work diligently at the outset, and through the review process, to understand the information pertaining to patient preference, risk/benefit frameworks, and other activities that will provide a more complete perspective of the patient experience with regard to any disorder, to the extent such materials and resources exist.

Specifically, MDA recommends that ICER undertake a process at the outset of each review whereby you work with the appropriate stakeholders including patient advocacy organizations to conduct a cursory review of information that is already available to inform ICER of the current needs and challenges that confront patients. We suggest that you look to umbrella organizations

like MDA and the National Organization for Rare Disorders (NORD) that can help ICER identify all relevant single disease patient advocacy organizations that may be able to offer valuable insights as you define the scope of your reviews. MDA also recommends that, whenever possible, you closely review all applicable materials that have been generated through the Food and Drug Administration's (FDA) Patient Focused Drug Development (PFDD) program. This program, led by the FDA's Center for Drug Evaluation and Research, captures meaningful data on patient experience and priorities. The reports, surveys, and web recordings from PFDD efforts are publicly available and contain valuable information shared directly from patients which would meaningfully inform ICER in its reviews. Through this process, ICER will likely learn of multiple disease registries that also contain insights and, in some cases, data sets that can also yield important findings. For example, MDA and many other organizations maintain robust patient registries. MDA's registry, the MOVOR (neuroMuscular ObserVational Research) Data Hub, is one such example. We encourage ICER to build enough lead time into your review process in order to engage with patient advocacy organizations that maintain registries so that, whenever possible, information gathered by them can be utilized to inform your work.

With regard to QALYs and other ways to measure impact and value, as ICER acknowledges in the Value Assessment Framework, there are myriad ethical issues that must be considered when assessing and opining on value. MDA encourages you to also include patients, their advocates, and clinicians in the public meeting voting process in order to meaningfully take their perspective and experience into account.

The value of a therapy that saves the lives of patients with a deadly rare disease is more complex than simple economics and cannot be measured without meaningfully engaging the patient community. We strongly urge you to ensure that the voices of those living with the disorder you are evaluating treatment for are considered at the outset of your work, from the initial scoping process to the publication of your final reviews. MDA appreciates this opportunity to provide input on ICER's Value Assessment Framework and we thank you for your consideration of the comment we have offered. If you have any questions about the information provided herein, please contact me at advocacy@mdausa.org.

Sincerely,

Brittany Johnson Hernandez
Senior Director of Policy and Advocacy
Muscular Dystrophy Association



National Health Council

1730 M Street NW, Suite 500, Washington, DC 20036-4561 ■ 202-785-3910 ■ www.nationalhealthcouncil.org ■ info@nhcouncil.org

BOARD OF DIRECTORS

Chairperson
Steve Taylor

Sjögren's Syndrome Foundation

Chairperson-Elect
Ann Palmer

Arthritis Foundation

Vice Chairperson
Gary M. Reedy

American Cancer Society

Secretary
Matt Eyles

America's Health Insurance Plans

Treasurer
Cassandra McCullough

Association of Black Cardiologists

Immediate Past Chairperson
Robert T. Gebbia

American Foundation for Suicide Prevention

Nancy Brown

American Heart Association

Tracey D. Brown, MBA, BChE

American Diabetes Association

LaVarne A. Burton

American Kidney Fund

Chester "Chip" Davis Jr., JD

Association for Accessible Medicines

Elizabeth Fowler

Johnson & Johnson

Patricia Furlong

Parent Project Muscular Dystrophy

Diana Gray

Hydrocephalus Association

Dory Kranz

National Alopecia Areata Foundation

Harold Paz, MD, MS

Aetna

Richard Pops

Alkermes, Inc.

Susan Sherman, MHA

The LAM Foundation

Lisa Simpson, MB, BCh, MPH, FAAP

Academy Health

Stephen J. Uhl

Pharmaceutical Research
and Manufacturers of America

Ex Officio Member
Marc Boutin, JD

Chief Executive Officer
National Health Council

June 10, 2019

Steven D. Pearson, MD, MSc

Founder and President of the Institute for Clinical and Economic Review
Institute for Clinical and Economic Review

Two Liberty Square, Ninth Floor, Boston, MA 02109

Comments on 2020 Framework

Dear Dr. Pearson:

The National Health Council (NHC) is pleased to provide comments on the Institute for Clinical and Economic Review's (ICER) solicitation for feedback on the 2020 Value Assessment Framework. Founded in 1920, the NHC is the only organization that brings together all segments of the health community to provide a united voice for the more than 160 million people in the United States with chronic diseases and disabilities, and their family caregivers. Made up of more than 125 diverse national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient advocacy organizations, which control its governance and policy-making process. Other members include health-related associations and nonprofit organizations including the provider, research, and family caregiver communities and businesses representing biopharmaceutical, device, diagnostic, generic, and payer organizations.

Both ICER and the NHC share a mutual goal of promoting increased access to affordable, high-value, sustainable health care. While important progress has been made, there is still significant work needed to fully integrate the patient voice into value assessment.

In July 2018, the NHC held a dialogue meeting of patients and patient groups with US value assessment (VA) bodies to articulate a shared vision for what marks success in patient-centered VA and to discuss what patient groups and value assessors can do, individually and together, to make value assessment more patient centered. We are pleased to note that ICER participated in that dialogue. Patient groups and VA bodies agreed: the ultimate goal of patient-centered VA is for patients to have access to treatments they need at prices they can afford. Patient-centered VA exists when patients have been engaged, heard, understood, and respected throughout the entire process, and their input is incorporated and guides

decision-making. Several of our suggestions below come from the recommendations we arrived at that day, and we hope you will consider them. The full report can be found on our website.¹

I. Understanding the Diversity of Patient Experience and of What Matters Most to Patients

ICER's current framework takes on a "population" level perspective, stating that recommendations are intended to support "broad guidelines on appropriate care, pricing, insurance coverage determinations, and payment mechanisms." While ICER recognizes the tensions this presents, it is important to acknowledge that broad-stroke recommendations have real impacts on heterogeneous patients' access to care in the real world. To mitigate this concern, we recommend that ICER provide separate recommendations for important subpopulations. These subpopulations may differ, not only in individual characteristics, but also in ideal treatment approaches. This distinction should be made clearer.

To that end, we encourage ICER to more systematically consider how diagnostic, prognostic, and predictive tests, which will become increasingly important for stratifying patient populations to receive optimal care, are incorporated into assessments.²

Patient engagement should inform a value assessment's PICOTS framework at the time of scoping.

Patient groups are experts on the condition they represent. They understand the heterogeneity of their constituents, and many groups have patient registries intended to capture diverse natural history of disease experiences and interactions with the health care system. As was recommended by the NHC dialogue participants, a relatively simple way to ensure that heterogeneity of patient populations is adequately incorporated into value assessment would be to engage patient groups and incorporate data from their natural-history-of-disease studies when developing the value assessment PICOTS framework (population, intervention, comparator, outcome, time, setting). ICER's use of the PICOTS framework and communicating publicly, and with patient groups from which ICER seeks information, to populate the PICOTS framework is one way of standardizing communications and conveying clearly the information patient groups could bring to the table in engaging with value assessors. This early, up-front engagement can also ensure that the value assessment (including the assessment of net clinical benefit) relies on evidence or assumptions that the patient community believes represent its lived experiences rather than a clinician or researcher's interpretation. This is especially important in defining subgroups. Agreement on the PICOTS framework as a communication tool can also contribute to ICER's decision regarding whether sufficient evidence is available to initiate an assessment. A lack of data may indicate a potential need and role for real-world evidence (RWE) and/or that additional time is needed for trial findings to become available.

Finally, to ensure that economic models align with patient-centered PICOTS frameworks, ICER should provide sufficient time for researchers to develop *de novo* models rather than rely on existing models due to time constraints.

Greater acceptance of additional research designs is needed to understand what matters most to patients.

Systematic literature reviews are conducted by ICER to identify relevant studies to perform the assessment. Importantly, these reviews are limited to studies on the intervention(s).³ ICER should consider the role of qualitative and quantitative preference studies, and other research stemming from patient-generated data sources. For example, the methods the US Food and Drug Administration (FDA) recommends for eliciting concepts important to patients are qualitative

(e.g., focus groups, interviews).⁴⁻⁷ Outcomes researchers have published extensively on how qualitative methodologies should be used for concept elicitation.⁸⁻¹¹ Additionally, CADTH has developed and tested methods for identifying these data, for example with their perspectives and experiences of patients and caregivers (PEPC) literature search filter.¹²

In addition to endorsing qualitative research for these purposes, we recommend that ICER describe the role that preference studies and real-world evidence (RWE) can play. In addition to ICER's own RWE framework, consideration of the FDA's recent guidance on using RWE for regulatory consideration can be a useful guide to ensuring ICER captures in its work the breadth of rigorous RWE studies available, which can in turn improve patient centricity by better reflecting the breadth of patient populations and their experiences with care.^{13,14} The International Society for Pharmacoeconomics and Outcomes Research and the International Society for Pharmacoepidemiology Task Force recommendations also describe approaches to ensure rigor in RWE.^{15,16} Given the lack of generalizability in clinical trial populations, RWE may be the only opportunity to glean insights on the effectiveness of treatments among certain subpopulations.¹⁷ As ICER seeks to understand the diversity of patient experiences, it is critical ICER develops a formal process for incorporating RWE into appraisals, and acknowledge when reports lack this type of evidence, so as to indicate gaps in available data and/or assumptions supporting the value assessment.

II. Incorporating Patient-Generated Evidence

Partner with patient groups to understand realistic timeframes and information needs.

It is important patient groups are contacted far enough in advance, so they have an opportunity to respond adequately. Two to three weeks does not grant enough time for any group, much less a small patient group with minimal resources, to be appropriately responsive to an ICER request. Patient groups may need to convene scientific or medical advisory boards of volunteers or engage large numbers of patients to gather sufficient data to be responsive. A few weeks is typically not sufficient timing to make this possible. Additionally, ICER should consider adapting its timeline and approaches to accommodate the real world in which voluntary health agencies operate, with lean staff numbers, limited in-house staff with related scientific expertise, and limited budgets for hiring consultants who can help them be as responsive and timely as they would like to be.

ICER can partner with patient groups to ensure that communications are optimal and are reaching the patient community effectively. Additionally, earlier awareness could be achieved through innovative approaches. For example, CADTH issues calls for patient input through Twitter. We again encourage ICER to consider these issues and the NHC stands ready to assist in implementing approaches that can help patient groups be engaged in a time-sensitive manner.

Clearly state information needs and acceptable study characteristics.

We are pleased that ICER increasingly provides opportunities for patients to engage throughout a VA and to submit data. To complement ICER's Patient Open Input Questionnaire, ICER should clearly emphasize and describe the patient-provided information that would be valuable for patient groups to collect pro-actively. The earlier that patient groups are aware of the need for surveys and other input/data collection, the better they can accommodate these requests. Data quality may also be improved. For example, it may be possible for patient groups to incorporate additional questions into existing patient registries and collect data over time rather than cross

sectionally in conjunction with a VA. Identifying and providing templates and tools from past data-collection efforts that were successfully incorporated into an appraisal (e.g. copy of successful survey) could be very useful and informative to the patient community.

Additionally, informing patient groups well in advance if submitted survey data need to have been published in a peer-reviewed journal would help all patient groups begin collecting and publishing data in advance of VA. Again here, earlier is better. The NHC and its membership is open to co-developing a guide to help patient groups with this process.

Impact of patient input and patient-group-submitted data should be clearly stated.

In addition, the impact of patient engagement or patient-group-submitted data is often unclear. We recommend ICER clearly state why and how patient input was or was not used in each report (if contributed). This feedback to groups will result in improved data contributions in the future.

Additionally, providing case examples where patient-experience input was demonstrated to have an impact on a value assessment could also be a valuable learning tool for other groups. Examples within health technology assessment have been provided in Canada, the United Kingdom, and elsewhere.^{18–22}

Debrief with patient groups after a report is complete.

Once an appraisal has been performed, it would be helpful if ICER and patient groups debrief on how submitted data were or were not useful in the end. As ICER begins the process of “re-reviews,” this grants the opportunity to investigate how data collection or presentation can be improved moving forward.

III. Methods to Integrate Dimensions of Value not Captured by the QALY

Quality-adjusted life year-based approaches are insufficient for capturing value from the patient perspective – shortcomings must be clearly articulated.

Both the NHC and ICER recognize the issues and implications of the quality-adjusted life year’s (QALY) limitations. Indeed, there are myriad methodological, ethical, and theoretical challenges associated with the QALY.^{23–26} ICER’s proposed alternative approach, the Equal Value of Life Years Gained (evLYG), is a welcome step toward addressing these important limitations. However, the evLYG is insufficient to overcome broader concerns with the QALY. Patient concerns with the QALY include but are not limited to discrimination based on quantity of life years gained. Ultimately, the evLYG is simply an additional sensitivity analysis that again does not adequately capture important components of value to the patient.²⁷ The NHC encourages continued methodological exploration to overcome these limitations.

In parallel to continued consideration of methods that move beyond the confines of the QALY and evLYG, ICER must clearly and adequately describe uncertainty and caveats associated with QALY-based approaches. It is essential that underlying populations, timeframe, and assumptions, from which health utilities are calculated, be transparent and clearly stated within the report.

We seek to avoid circumstances such as those that have been reported where a cost/QALY number will be used as the sole determinant of value rather than as an input to a thoughtful

decision-making process. While we understand fully that ICER cannot be responsible for a user's misuse of a value assessment report's findings, we implore ICER to be responsible in how it presents findings so that intentional cherry picking of results, especially in a way that hurts patients, is clear.

Societal and public-payer perspectives are key.

ICER presents the health system perspective for its base case and has previously described that it does not intend to provide a full societal perspective despite the Second Panel on Cost Effectiveness' recommendation to do so.²⁸ The recent ICER draft evidence report on Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy: Effectiveness and Value found that the "addition of societal costs notably decreased the incremental cost-effectiveness ratios at each value-based price anchor point."²⁹ This additional context is critical for interpreting findings based on a health system perspective. It may also provide key information for certain payers, especially employers where caregivers could be the employees. Similarly, public payers should consider how investments in healthcare can help to alleviate poverty and disability more broadly. As public payers have expressed interest in using ICER reports to inform coverage decision-making, ICER should urgently consider the adequacy of a health system perspective.³⁰

IV. Conclusion

The NHC appreciates the opportunity to comment on ICER's initiative and agrees that in this emerging field, methods must evolve and will need to be updated/adapted as experience in this space grows. We are excited by and hopeful that patient-focused drug development will yield clinical-trial data that is more patient centered, focusing on experiences of and outcomes important to patients. This will improve data sources for patient-centered value assessment in the future.

The recommendations made above are offered with the goal of increasing patient centrality in health technology assessment. The NHC appreciates ICER's work to more proactively involve the patient community in value assessment. Just as opportunities to engage have increased in recent years, we hope to see a greater impact of patient engagement on value assessment moving forward.

We at the NHC are happy to discuss these recommendations with you, to clarify any suggestions we've made and to hear from you about how we can be supportive of their implementation. As always, please do not hesitate to reach out to us by contacting Elisabeth Oehrlein, PhD, MS, our Senior Director of Research and Programs, at 202-973-0540 or via email at eoehrlein@nhcouncil.org.

Sincerely,

Marc Boutin, JD
Chief Executive Officer
National Health Council

References

1. A Dialogue on Patient-Centered Value Assessment: Overcoming Barriers to Amplify the Patient Voice. National Health Council. <https://www.nationalhealthcouncil.org/dialogue-patient-centered-value-assessment-overcoming-barriers-amplify-patient-voice>. Published November 30, 2018. Accessed March 11, 2019.
2. Pritchard D. Personalized Medicine Coalition Comments on Proposed Updates to the Value Assessment Framework. <http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PMC-ICER-Proposed-Updates-4.3.17.pdf>. Accessed May 30, 2019.
3. Institute for Clinical and Economic Review. A Guide to ICER's Methods for Health Technology Assessment. http://icer-review.org/wp-content/uploads/2018/08/ICER-HTA-Guide_082018.pdf. Published August 2018. Accessed May 29, 2019.
4. Research C for DE and. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. Food and Drug Administration. <http://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims>. Published April 21, 2019. Accessed May 29, 2019.
5. Research C for DE and. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. U.S. Food and Drug Administration. <http://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input>. Published December 1, 2018. Accessed May 29, 2019.
6. Food and Drug Administration. *Methods to Identify What Is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments*. White Oak, MD; 2018. <https://www.fda.gov/media/116276/download>. Accessed May 29, 2019.
7. Food and Drug Administration. Roadmap to Patient-Focused Outcome Measurement in Clinical Trials. <https://www.fda.gov/media/87004/download>. Accessed May 29, 2019.
8. Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1--eliciting concepts for a new PRO instrument. *Value Health*. 2011;14(8):967-977. doi:10.1016/j.jval.2011.06.014
9. Brédart A, Marrel A, Abetz-Webb L, Lasch K, Acquadro C. Interviewing to develop Patient-Reported Outcome (PRO) measures for clinical research: eliciting patients' experience. *Health Qual Life Outcomes*. 2014;12:15. doi:10.1186/1477-7525-12-15
10. Lasch KE, Marquis P, Vigneux M, et al. PRO development: rigorous qualitative research as the crucial foundation. *Qual Life Res*. 2010;19(8):1087-1096. doi:10.1007/s11136-010-9677-6
11. Humphrey L, Willgoss T, Trigg A, et al. A comparison of three methods to generate a conceptual understanding of a disease based on the patients' perspective. *Journal of Patient-Reported Outcomes*. 2017;1(1):9. doi:10.1186/s41687-017-0013-6
12. Rader T, Farrah K, Kaunelis D. Things Go Better with PEPC: Testing the Performance of Patient-Related Literature Search Filters. Presented at the: 2016 CADTH Symposium; April 11, 2016; Ottawa, ON.
13. Health C for D and R. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. U.S. Food and Drug Administration.

<http://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices>. Published April 9, 2019. Accessed May 29, 2019.

14. Pearson SD, Dreitlein WB, Towse A, Hampson G, Henshall C. A framework to guide the optimal development and use of real-world evidence for drug coverage and formulary decisions. *Journal of Comparative Effectiveness Research*. 2018;7(12):1145-1152. doi:10.2217/cer-2018-0059
15. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiol Drug Saf*. 2017;26(9):1033-1039. doi:10.1002/pds.4297
16. Wang SV, Schneeweiss S, Berger ML, et al. Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0. *Pharmacoepidemiol Drug Saf*. 2017;26(9):1018-1032. doi:10.1002/pds.4295
17. Hampson G, Towse A, Dreitlein WB, Henshall C, Pearson SD. Real-world evidence for coverage decisions: opportunities and challenges. *Journal of Comparative Effectiveness Research*. 2018;7(12):1133-1143. doi:10.2217/cer-2018-0066
18. Facey KM. As health technology assessment evolves so must its approach to patient involvement. *Journal of Comparative Effectiveness Research*. May 2019. doi:10.2217/cer-2019-0039
19. Facey KM, Bedlington N, Berglas S, Bertelsen N, Single ANV, Thomas V. Putting Patients at the Centre of Healthcare: Progress and Challenges for Health Technology Assessments. *Patient*. 2018;11(6):581-589. doi:10.1007/s40271-018-0325-5
20. Facey K, Hansen HP, Single A, eds. *Patient Involvement in Health Technology Assessment*. ADIS; 2017. <https://www.springer.com/gp/book/9789811040672>. Accessed May 29, 2019.
21. Abelson J, Bombard Y, Gauvin F-P, Simeonov D, Boesveld S. Assessing the impacts of citizen deliberations on the health technology process. *Int J Technol Assess Health Care*. 2013;29(3):282-289. doi:10.1017/S0266462313000299
22. Staley K, Doherty C. It's not evidence, it's insight: bringing patients' perspectives into health technology appraisal at NICE. *Res Involv Engagem*. 2016;2. doi:10.1186/s40900-016-0018-y
23. Neumann PJ, Cohen JT. QALYs in 2018—Advantages and Concerns. *JAMA*. 2018;319(24):2473-2474. doi:10.1001/jama.2018.6072
24. Pettitt DA, Raza S, Naughton B, et al. The limitations of QALY: a literature review. *Journal of Stem Cell Research and Therapy*. 2016;6(4). <https://ora.ox.ac.uk/objects/uuid:d22a9b1b-c2f0-4f6c-83ee-fdc320e4af61>. Accessed March 15, 2019.
25. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *Br Med Bull*. 2010;96:5-21. doi:10.1093/bmb/ldq033
26. Prieto L, Sacristán JA. Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual Life Outcomes*. 2003;1:80. doi:10.1186/1477-7525-1-80

27. Will ICER's Response to Attacks on the QALY Quiet the Critics? - Center for the Evaluation of Value and Risk in Health. <https://cevr.tuftsmedicalcenter.org/news/2018/will-icers-response-to-attacks-on-the-qaly-quiet-the-critics>. Accessed May 29, 2019.
28. ICER-value-assessment-framework-Updated-050818.pdf. <http://icer-review.org/wp-content/uploads/2017/06/ICER-value-assessment-framework-Updated-050818.pdf>. Accessed May 29, 2019.
29. Institute for Clinical and Economic Review. Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy: Effectiveness and Value Draft Evidence Report (April 9, 2019). https://icer-review.org/wp-content/uploads/2018/10/ICER_PeanutAllergy_Draft_Evidence_Report_040919.pdf. Published April 9, 2019. Accessed May 30, 2019.
30. Thomas K. A Drug Costs \$272,000 a Year. Not So Fast, Says New York State. *The New York Times*. <https://www.nytimes.com/2018/06/24/health/drug-prices-orkambi-new-york.html>. Published June 25, 2018. Accessed May 30, 2019.

June 10, 2019

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: The 2020 Update to ICER's Value Assessment Framework

To Whom It May Concern:

The National Hemophilia Foundation (NHF) and Hemophilia Federation of America (HFA) are national non-profit organizations that represent individuals with bleeding disorders across the United States. Our missions are to ensure that individuals affected by hemophilia and other inherited bleeding disorders have timely access to quality medical care, therapies, and services, regardless of financial circumstances or place of residence. Both organizations accomplish this through advocacy, education, and research.

We appreciate the opportunity to provide comment to the Institute for Clinical and Economic Review (ICER) on its 2020 update to the Value Assessment Framework. We are pleased to submit comments on the following subjects:

Understanding the Diversity of Patient Experience and What Matters Most to Patients

We appreciate that ICER is seeking to better understand diverse patient populations and incorporate patient-important outcomes into its reviews. Thank you for your continued interest and for seeking to understand the patient perspective and the unique value it brings to your deliberations. We believe the patient voice must be included at every stage of product development and evaluation, from identification of research topics through research design, clinical trials, long-term follow-up, and ultimately health technology assessment and payer decision-making. It is important to take note that the highly curated population of study participants within clinical trials may not reflect the full diversity of the wider patient population living with the disease or condition at issue. To facilitate a wider understanding that is adaptable to real-world settings, the global bleeding disorders community has developed several value-based frameworks and patient-reported outcome tools, which have been discussed and validated in peer-reviewed literature. We understand that other patient communities are embarking on similar processes. We encourage you to review and include relevant metrics from these tools and the data they provide in your assessments.

Incorporating Patient-Generated Evidence and Integrating Dimensions of Value not Captured by the QALY

In prior letters, we have encouraged you to broaden your economic models to reflect all critical elements, including patient-important outcomes. To fully realize the goal of patient-centered care, value should also be assigned to the societal burden and indirect burdens/costs borne by those living with the disease across their lifespans. Inclusion of elements that account for health equity and societal value would be both timely and responsive to contemporary policy dialogues on healthcare system reform. These new elements will be especially important in valuation of the transformative potential for curative technologies, in contrast to existing standard of care. We do not believe cataloging these elements as “Other benefits or Contextual Considerations” at the end of a report sufficiently reflects their importance. Economic models should give due consideration to both direct health care costs and indirect burdens/costs affecting patients and caregivers. Ideally, these considerations should be included within the base case analysis. When not possible, scenario analysis should be presented in parallel.

As part of ICER’s update to the value framework it is timely to rethink how long-term value is calculated. While the recent inclusion and reporting of the evLYG measure in addition to the QALY brings a welcome new dimension to the ICER reports, we are mindful that this addresses just one component and the QALY is still viewed as the gold standard in cost-effectiveness analysis. Therefore, we renew our request that ICER consider directly including the use of appropriate discount rates within the base case analysis to account for the **long-term value** of health effects in relation to costs. Health technology assessment agencies in the UK and France, among others, utilize variable discount rates. The QALY calculation should be modified to capture the benefit reflecting a lifetime of health, beyond the timespan of limited short-term interventions.

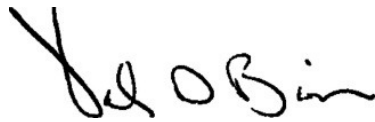
We recognize many of the benefits we are suggesting for inclusion within the model may be challenging to measure, and that data may not be attainable within the limited time of a clinical trial. We also appreciate ICER’s positive comments about the important role patient communities play in filling gaps in the ICER assessments. Over recent years, our organizations have worked diligently to address this void through development of robust and comprehensive metrics and data collection frameworks that capture outcomes important to patients. Much of this work has now been validated and published in the scientific literature. ICER value framework data inputs should encourage maximal inclusion of indirect evidence, registry, and patient generated data. This is particularly important in rare and ultra-rare diseases such as hemophilia and related bleeding disorders, where critical data on outcomes important to patients is often limited or not available from clinical trial data or in published literature. Greater tolerance for uncertainty may be warranted to achieve a more comprehensive assessment.

Ultra-Rare Framework

We reiterate the concerns we have previously raised regarding ICER's employment of an arbitrary – and very low - number threshold rather than making an assessment to the quality of the evidence for a particular condition before deciding whether the adapted framework is appropriate. We agree with those who argue that additional factors, such as severity and potential for a significant gain in quality or length of life, should be considered, rather than just the number of affected people. ICER has not sufficiently justified why the threshold is so low, nor why the standard would be rigidly implemented. We were pleased that ICER used its ultra-rare framework for its 2017 review of emicizumab for hemophilia A with inhibitors, and encourage ICER to change its policy to apply the ultra-rare adaptations more broadly than just for conditions with fewer than 10,000 individuals.

We appreciate the opportunity to provide these comments and thank you for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read 'Val Bias', written in a cursive style.

Val Bias
Chief Executive Officer
National Hemophilia Foundation

A handwritten signature in black ink, appearing to read 'Kimberly K. Haugstad', written in a cursive style.

Kimberly Haugstad
President & CEO
Hemophilia Federation of America



June 10, 2019

Steven Pearson, MD, MSC, FRCP
President
Institute for Clinical and Economic Review
Boston, MA 02109

Via electronic mail: publiccomment@icer-review.org

Dear Dr. Pearson,

The National Multiple Sclerosis Society (Society) appreciates the opportunity to provide input to inform the development of the Institute for Clinical and Economic Review's (ICER) 2020 Value Assessment Framework (framework). The Society works to provide solutions to the challenges of multiple sclerosis (MS) so that everyone affected by this disease can live their best lives. To fulfill this mission, we fund cutting-edge research, drive change through advocacy, facilitate professional education, collaborate with MS organizations around the world, and provide services designed to help people affected by MS move their lives forward.

The Society applauds ICER for seeking public input to inform the development of the 2020 assessment framework. As the use of value assessment in health care evolves, ensuring that patient preferences and experience are fundamental components of the assessment of value is critical. Without this information, it is difficult to fully assess value in a way that will improve health outcomes and adherence. We are encouraged that ICER is committed to adapting its model to reflect the evolving role of value in the health care cost discussion. We recommend that ICER direct each of its voting committees to first examine and vote on contextual considerations that are informed by patient preferences and experience before their review and vote on the clinical evidence. As the full breadth of evidence is not incorporated into the clinical evidence review and vote, we believe holding the first vote on contextual considerations will better keep key considerations from patients in the forefront as the committee votes on the clinical evidence that was presented.

Understanding the Diversity of Patient Experience and of What Matters Most to Patients

The Society believes that patients should be viewed as the experts in how they manage their disease and the impact of their disease on their lives. Likewise, patient groups should be viewed as experts and resources on the condition they represent. As a member of the National Health Council (NHC), we endorse their recommendation that the learnings from patient engagement should inform ICER's value assessment's PICOTS framework (population, intervention, comparator, outcome, time, setting) at the time of scoping and urge ICER to incorporate these recommendations. ICER should directly engage with patient groups when it seeks information to populate the PICOTS framework, ensuring that the value assessment relies on evidence or assumptions that represent their real life experience. We also concur with the NHC's recommendation that ICER can ensure that heterogeneity of patient populations is adequately incorporated into value assessment by engaging patient groups and incorporating data from their natural-history-of-disease studies when developing the value assessment PICOTS framework. As ICER reviews do have real world implications for people who rely on the medications and treatments under review, we believe it is important to reach agreement with relevant patient groups on the PICOTS framework and ICER's view regarding

whether sufficient evidence is available to initiate an assessment. A lack of data may indicate a potential need and role for real-world evidence (RWE) and/or that additional time is needed for trial findings to become available.

Greater acceptance of additional research designs is needed to understand what matters most to patients

The Society believes ICER's framework would be greatly enhanced by incorporating additional types of research to inform its work. We implore ICER to consider diversity in the evidence utilized in their reviews, especially in disease areas where data are limited. The insistence that quality adjusted life year (QALY) is the gold standard and what feels like an overreliance on published clinical trial data means that ICER is missing key perspectives and data in its' value assessments.

Clinical Trial Data and Real World Evidence

To date, ICER has relied upon published clinical trial data to inform the value assessment framework. The Society has previously commented to ICER the problems with utilizing this data for comparative purposes, particularly when the comparison is between two completely different studies. As understanding of a disease state evolves, clinical trials to confirm safety and efficacy of a potential treatment will evolve as well. Clinical trial populations will become more reflective of the disease population (including demographic subgroups), and new primary and/or secondary outcome measures may be added. The Society believes ICER's methodology must be able to adapt and account for these evolutions. Currently, the methodology has limited ability to adapt to these evolutions as it solely relies on clinical trial data to inform the model. For example, in MS, the Expanded Disability Status Scale (EDSS) has long been used as a measure of disability progression. It is now recognized that EDSS focuses on mobility and physical disability, and that cognition and fatigue are significant measure that matter to people with MS. Some clinical trials have begun to measure cognition, and we believe this measurement will become more prevalent in future trials. Early trials in MS did not measure cognition, making a meta analysis across all trials difficult to incorporate this important information.

Additionally, ICER has used comparisons based on "usual care." In some cases, the "usual care" that ICER proposes does not align within the context of present treatment practice. Data used in this way is in effect a pseudo-placebo condition which again, involves completely separate studies or data not collected in the context of a randomized controlled trial.

While ICER has stated openness to including other types of data like real world evidence (RWE), we have not seen other data sources included in MS reviews. ICER has invested in policy discussions on the use of real world evidence for coverage and formulary decisions, and we encourage ICER to similarly describe the role that RWE can play in informing the value assessment framework and set clear parameters for RWE that would be included in ICER assessments. The Food and Drug Administration's (FDA) recent guidance on using RWE for regulatory consideration can be a useful guide to ensuring ICER captures the breadth of rigorous RWE studies available, which will improve the patient centricity of ICER's reviews¹. The International Society for Pharmacoeconomics and Outcomes Research and the International Society for Pharmacoepidemiology Task Force recommendations also describe approaches to ensure rigor in RWE^{2,3}. Given the lack of generalizability in clinical trial populations, RWE may be the only opportunity to systematically assess effectiveness of treatments among certain subpopulations outside of a controlled clinical trial environment. As ICER seeks to understand the diversity of

patient experiences, it is critical ICER develops a formal process for incorporating RWE into appraisals.

Risk/Benefit and Other Patient Preference Studies

Currently, most data being used by ICER for comparison does not include the patient perspective, including patient views on the balance of risk and benefit when identifying a treatment that aligns with their goals. The Society recommends that ICER should describe the role that risk/benefit, preference studies and willingness to pay studies can have in informing the value assessment framework. These types of data would be very helpful in each ICER committee understanding the relevant disease state including impact of disease, perceptions of treatment and factors important to patients in weighing treatment options. Data regarding patient perspectives on a treatment's risk and benefit should be incorporated to refine analysis using quality adjusted life year (QaLY)'s and equal value of life years gained (evLYG)'s. The treatment experience from the patient perspective is a complex mix of anticipation of benefit, progress toward symptom relief, disappointment, adverse events, financial burden, uncertainty, and mortality risk. To fully capture all of these issues, ICER would need to address them with data from patient's perspective directly, not as the patient experience that is informed by a researcher or clinician. In our opinion, ICER should at least include data on patient willingness to pay and disability adjusted life years (DaLY's) as a part of its scoping. It is understandable that ICER is reluctant to incorporate perspectives outside of the generally accepted methodology based on QaLY's.; however, not doing so misses an important opportunity to explore potentially meaningful insights that will improve the value assessment framework.

Incorporating Patient-Generated Evidence

As the Society referenced in its comments on ICER's 2017 value assessment framework, we believe that a major flaw of the current iteration of the value assessment framework is the limited way that it addresses the incorporation of the patient perspectives. Although patients have been incorporated in the process, their role is as "outsiders" invited to suggest and comment. Instead, patients should be a fundamental working as part of the ICER team from before the scoping process. We recommend that ICER, before scoping begins on a potential assessment, incorporate patients, patient groups, care partners, health care providers and family members in all phases of the value framework planning and analysis as full and active partners.

Additionally, when patient-generated evidence is included, we recommend that ICER be clear and transparent about how this evidence helps to inform the economic model.

The Society recommends that ICER consider utilizing both qualitative and quantitative preference studies, and other research stemming from patient-generated data sources. We recommend that ICER work closely with the Patient Centered Outcomes Research Institute (PCORI) and incorporate their model into the ICER value assessment process. The PCORI model views patients as core partners in the scientific endeavor rather than subjects alone. This means that the patient perspective cannot come exclusively from a limited number of small and geographically limited focus groups or panel meetings. Focus groups and existing literature should be utilized as part of the development and implementation of the value framework but not in the absence of active and comprehensive patient participation in all phases of the work. PCORI has been a leader in creating a "gold-standard" for patient involvement in research studies and the Food and Drug Administration has worked closely with them to align their work in patient focused drug

development with PCORI standards for patient inclusion. For example, the methods the FDA recommends for eliciting concepts important to patients are qualitative (e.g., focus groups, interviews). Outcomes researchers have published extensively on proper methodologies for concept elicitation. Additionally, the Canadian Agency for Drugs and Technologies in Health has developed and tested methods for identifying these data, and ICER can reference these within their perspectives and experiences of patients and caregivers literature search filter.

III. Methods to Integrate Dimensions of Value not Captured by the QaLY

While QaLY is one of the most commonly used methods in cost-effectiveness, it is rarely referenced alone as “the gold standard”. In fact, most literature presents both the positives and negatives of relying on QaLY. We appreciate ICER’s willingness to integrate other dimensions of value. In prior correspondence, we had recommended that ICER should clarify its calculation of the QaLY, particularly as there are concerns that a cost-per-QaLY cannot adequately account for the value of substantially improving the life of a person with a disability or serious medical condition. A paper published in the *British Medical Bulletin* states that “QaLYs that occur in the future are discounted to current values, to incorporate the idea that people prefer to receive health benefits now rather than in the future”⁴. This illustrates one of the difficulties in solely utilizing QaLYs in a condition like MS, with treatments designed to improve the future state (through delay of disability progression). Additionally, patient concerns with the QaLY include, but are not limited to discrimination based on quantity of life years gained and failure to capture any patient perspective of value, and these limitations are well documented in the patient community and to ICER. For example, as stated previously in these comments, EDSS captures mobility and physical disability progression, but other critical domains like cognition and fatigue are not reflected as robustly based on utility scores alone. These domains are important not just to the individual with MS, but also from a societal perspective. People with MS with changes in employment status such as reduced work hours or prematurely leaving the workforce often cited fatigue or cognitive symptoms as the reasons for their employment change.⁵ We believe it is essential that underlying populations, timeframe, and assumptions from which health utilities are calculated be transparent and clearly stated within the report.

We appreciate ICER proposing an alternative approach in the equal value of life years gained (evLYG); however, the evLYG is insufficient to overcome broader concerns with the QaLY. Ultimately, the evLYG is simply an additional sensitivity analysis that again does not adequately capture important components of value to the patient. The Society echoes NHCs recommendation that ICER continue exploring methodological approaches to overcome these limitations. Additionally, we believe that ICER can play a meaningful role in moving the needle on what metrics should be used in value assessment. We believe ICER should fully commit to working with stakeholders from across the health economic, patient, and health care community to lead discussions around a metric that would be a gold standard to use for value assessment. In fact, ICER is uniquely positioned to create a task force to bring stakeholders together to move this essential work forward.

There are other value perspectives that could be incorporated into such a metric, including DaLY’s, risk/benefit, willingness to pay, out-of-pocket costs, indirect costs, comorbidities, device utilization and cost, social participation, family burden, and the context of care. While ICER currently addresses many of these issues as a part of their other benefits and contextual considerations section

of its report, full transparency about how each of these elements could be pulled through the value assessment framework will go a long way to clearing up the ambiguity as to how they are currently reflected and influence this section of an ICER review.

The Society remains concerned that ICER reports may be used to deny care and a cost/QaLY number will be used as a decision-making hatchet rather than as an input to a thoughtful decision-making process. We have seen instances where ICER reports have been used to limit care, and while we understand that ICER cannot control how payors utilize their findings, we do urge ICER to respond when others intentionally cherry-pick results to limit care options. Fully presenting its findings in context to relevant health questions is critical and will help build trust within the patient community around the concept of value assessment.

Thank you for the opportunity to share our comments on ICER's proposed updates to its value assessment framework and patient participation guide. Please do not hesitate to contact Leslie Ritter, Senior Director, Federal Government Relations at leslie.ritter@nmss.org or 202-408-1500 if you or your staff would like to discuss these issues in greater detail. We look forward to continued discussions around this topic.

Sincerely,



Bari Talente, Esq.
Executive Vice President, Advocacy

¹ Food and Drug Administration. "Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics". May 2019. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-utilizing-real-world-data-and-real-world-evidence-fda-drugs-and-biologics>

²The International Society for Pharmacoeconomics and Outcomes Research. Good Practices for Outcomes Research. <https://www.ispor.org/heor-resources/good-practices-for-outcomes-research>

³ Berger, M. et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiology & Drug Safety*. <https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.4297>.

⁴ Whitehead, Sarah and Ali, Shehzad. Health outcomes in economic evaluation: the QALY and utilities. *British Medical Bulletin* 2010; 96: 5-21. <https://academic.oup.com/bmb/article/96/1/5/300011>

⁵ Coyne, K. S., Boscoe, A. N., Currie, B. M., Landrian, A. S., & Wandstrat, T. L. (2015). Understanding Drivers of Employment Changes in a Multiple Sclerosis Population. *International journal of MS care*, 17(5), 245–252. doi:10.7224/1537-2073.2014-051



June 10, 2019

Institute for Clinical and Economic Review
Two Liberty Square
Ninth Floor
Boston, MA 02109

Re: ICER Seeks Public Input for 2020 Value Assessment Framework

Dear Dr. Pearson:

On behalf of the 25 to 30 million Americans with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Institute for Clinical and Economic Review (ICER or the Institute) for the opportunity to provide comments on the Institute's call for suggestions and feedback on how to improve its value assessment framework for 2020 and beyond.

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

NORD is also committed to fostering a health care ecosystem that encourages the development of, and affordable access to, safe and effective therapies for rare disease patients. In May 2019, NORD issued a document entitled "[Principles for Assessing Proposals Designed to Lower the Cost of Prescription Drugs in the United States](#)." These principles are intended to provide transparency around NORD's evaluation of proposed public policies for lowering the cost of therapies for our patients. They illustrate NORD's commitment to ensuring our patients can access innovative therapies.

In general, NORD believes that therapies should be priced based upon the value that they bring to patients, their families, and our health system as a whole. However, NORD further believes that the sustainability of the health care system and the existing social and economic inequities that could be exacerbated by high medical costs must also be considered. ICER and other similar entities serve a valuable function in ensuring these goals are achieved. These organizations conduct empirical analyses to assess the value a particular product brings to insurers, patients, and our society as a whole, yet these analyses are only beneficial if they fully incorporate patient perspectives and experiences.

We are pleased to oblige ICER's call for comments on their general value assessment framework, ultra-rare value assessment framework, and patient participation guide. Overall, we acknowledge and applaud ICER for the improvements to date in its evaluations and processes. NORD remains concerned about specific aspects of ICER's reviews that could result in detrimental access challenges for our patients.

Definition of an "Ultra-Rare Condition" as any Population of Fewer than 10,000 Individuals:

NORD continues to be concerned with ICER's approach to subdividing the rare disease community into ultra-rare and non-ultra-rare conditions. As outlined in NORD's September 2017 comments on the proposed ultra-rare framework, NORD has long opposed efforts to subdivide the rare disease community into smaller subsets of patient populations. For example, we expressed our concern with the Food and Drug Administration (FDA or Agency) when, in a July 2018 draft guidance on "Slowly Progressive Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies," the Agency defined a "low-prevalence rare disease" in the context of the guidance as any disease with fewer than 5,000 individuals.¹

Our concerns with subdividing the community stem from the belief that such policies would do more harm to the rare disease patient populations that do not fall within the "ultra-rare" category than good for the rare disease patient populations that do. We fear that those rare diseases that are excluded would be considered no differently than common diseases and the challenges that arise due to rare, but not "ultra-rare," patient populations would be ignored and discarded.

In the context of ICER's assessments, we are concerned that the rare diseases (defined by the Orphan Drug Act as any disease affecting fewer than 200,000 individuals in the United States) that are excluded from the ultra-rare framework will not receive the same flexible and progressive review offered to "ultra-rare" conditions, which could potentially adversely affect their review.

Many of the orphan drugs reviewed by ICER have been reviewed using the "ultra-rare framework." These include deflazacort, eteplirsen, and golodirsen for Duchenne muscular dystrophy; inotersen and patisiran for amyloidosis; ivacaftor for cystic fibrosis; and Ixekicimab and C1 esterase inhibitors for hereditary angioedema. However, ICER applied its general framework for other rare disease therapies, such as Hemlibra for hemophilia A and therapies for multiple myeloma.

NORD once again requests that ICER consider using its ultra-rare framework not just for diseases with a prevalence of fewer than 10,000 individuals but for all rare diseases. The cut-off of 10,000 individuals is arbitrary, and we disagree with ICER's original assertion for this cut-off that the "application of adapted methods of value assessment are not needed for the majority of 'orphan' drugs as defined by the Orphan Drug Act, as sufficient patient numbers are usually available for 'routine' clinical trials, and outcome measures are likely to be relatively standardized and well-documented."² Clinical trials are often quite difficult for rare diseases of all prevalence levels, and the challenges of developing outcome measures do not disappear at a prevalence of 10,001.

These same concerns also apply to ICER's disqualification from the ultra-rare framework that occurs when the patient population receiving the therapy is expected to eventually exceed 20,000 individuals. This rationale was initially used to exclude Hemlibra from the ultra-rare framework even though there are fewer than 10,000 individuals currently expected to take the therapy in the United States. However, ICER did end up using the ultra-rare framework in its final report.

¹ Melmeyer, P. (2018, September 25). Retrieved from <https://rarediseases.org/wp-content/uploads/2018/09/NORD-2018-Comments-on-Low-Prevalence-Final.pdf>

² Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions. (2017, July 25). Retrieved June 6, 2019, from https://icer-review.org/wp-content/uploads/2017/05/ICER_Proposed_VAF_Adaptations_Orphan_Drugs_072517.pdf

In summary, we strongly encourage ICER to take this opportunity to consider expanding its use of the ultra-rare framework to include all rare diseases, as defined by the Orphan Drug Act.

Willingness-to-Pay Thresholds in the Ultra-Rare Framework:

NORD remains supportive of ICER's approach to increasing the willingness-to-pay threshold up to \$500,000 per QALY within its ultra-rare framework. This higher threshold for willingness-to-pay has been applied appropriately throughout the various ultra-orphan reviews and has resulted in more nuanced and flexible reviews of these therapies.

For these reasons, we encourage ICER to continue to use the willingness-to-pay threshold of \$500,000 per QALY rather than the \$50,000 per QALY employed in the general framework.

Incorporation of Contextual and Non-Traditional Benefits and Values:

NORD continues to be appreciative of ICER's inclusion and consideration of contextual and non-traditional benefits of a therapy to the patient, their family, and caregivers. There are many benefits of a therapy that are generally not well-captured within traditional cost effectiveness analyses. These include quality-of-life (QOL) improvements for the patient, such as a better ability to sleep, better management of pain, and the ability to partake in employment and hobbies.

We are also thankful that ICER is specifically requesting feedback from patients and their organizations on how to incorporate patient generated evidence and "methods to integrate dimensions of value not captured by the QALY." Both of these topics are critically important to ensuring patient viewpoints and contextual and non-traditional benefits are incorporated. We hope that disease-specific organizations, particularly those who have already participated in an ICER review, will comment on their experiences and how ICER can improve the process of data collection going forward.

There are many potential ancillary benefits of therapeutic interventions to families and caregivers. Parents of children with rare diseases value the ability to sleep through the night, go back to work, socialize with friends, or take better care of their child. Caregivers also are benefited if their patient is healthier and happier. Further, societal benefits should be considered, including substantial advances in science and medicine.

Consequently, we thank ICER for considering these benefits as it evaluates therapies. However, as explained in our previous comments, we still encourage ICER to find ways to include these contextual and non-traditional benefits into the specific cost-per-QALY outcome of the evaluation. For example, ICER considered patient viewpoints and quality-of-life benefits in its review of treatments for spinal muscular atrophy, amyloidosis, hemophilia, and others. However, as evidenced in each of these reports, these "potential other benefits" were left to a separate, non-quantitative section of each ICER report, thus, allowing these considerations to be siloed away from ICER's final determination.

There are methodologies ICER can employ to incorporate not only non-traditional and contextual benefits to patients but also benefits to family members, caregivers, and society. In fact, ICER employed such methodologies in its assessment of Luxturna for a specific retinal blindness. In this assessment,

ICER evaluated Luxturna from both the health system and societal perspective, thus, allowing readers to ascertain the potential benefit of the therapy outside of strict cost-per-QALY, budgetary, and insurer-oriented structures.

While this is encouraging, and we again applaud ICER for moving in this direction, there were still many additional ways in which ICER could have better incorporated the “potential other benefits” that were again siloed in Luxturna’s report. Consequently, while we applaud ICER for its progress, we still encourage ICER to better incorporate patient, familial, and caregiver experiences and perspectives and the non-traditional value derived from orphan therapies.

Value-based Price Benchmark of \$100,000 to \$150,000 per QALY:

While NORD understands ICER’s desire to apply a uniform value-based price benchmark across all therapies regardless of the framework used, we still encourage ICER to consider either using a higher value-based price benchmark to acknowledge the additional non-traditional and contextual benefits orphan drugs often provide. Alternatively, ICER could keep the same price benchmark but better incorporate these benefits into the cost-per-QALY itself. If ICER chooses to exercise neither of these options, it will once again be ignoring value that patients, family members, and caregivers derive from these therapies.

Patient Participation Process:

NORD continues to be concerned by the arduous, time-consuming, and overly-expedited process in which patient organizations are expected to participate. NORD understands that ICER aims to review therapies on an iterative, thorough, and expedited timeline. Consequently, ICER requests that stakeholders, including those in the patient community, respond to substantial and content-rich documents, such as scoping documents and evidence reports, on a particularly accelerated timeline.

As representatives of the rare disease patient community, we are particularly concerned about the effect this has on rare disease patient organizations that represent communities for which a therapeutic review is being conducted. Many disease-specific organizations dread upcoming ICER reviews for their population as it will cause them to sacrifice work on many other programs and services for their communities. Organizations have had to drop other initiatives to spend a large proportion of their time and resources on participating in ICER reviews.

NORD asks that ICER consider ways to make their patient participation process less burdensome on the community. By doing so, ICER can accomplish one of its goals set forth in “A Patient’s Guide to Open Input” of ensuring that a diversity of patient experiences are collected.³ By requiring an extensive understanding of health economics, as well as substantial time and resources to participate, ICER is potentially excluding patients and patient organizations that could offer important input.

Therefore, NORD encourages ICER to consider ways to capture the voice of all patients and patient organizations in a particular disease space. This includes perhaps extending timelines for commenting (three weeks is often too short for a several-hundred-page document) and proactively reaching out to

³ The 2020 Update to ICER’s Value Assessment Framework: A Patient’s Guide to Open Input. Retrieved from https://icer-review.org/wp-content/uploads/2019/05/ICER_2020VAF_Patient_Guide_05212019.pdf

under-represented communities. We are appreciative that ICER's has viewed NORD as a resource when seeking patient organizations that represent certain populations, and we encourage ICER to continue to reach out if we can be at all helpful in ensuring patient voices are well represented.

Additionally, ICER should find ways to ensure that the patient perspective is adequately represented at public meetings. This includes facilitating remote patient participation for those who are unable to travel to the meeting to attend in-person. For those who are able to attend in-person, ICER should allow for a summary that is longer than 250-words to be submitted by oral presenters. Limiting patients to such a small written summary forces patient to present their experiences in ways they may not feel to be accurate or complete. We invite ICER to consider expanding the total word allowance, if not abolishing it all together, for patients, families, and caregivers.

We thank ICER for the opportunity to comment, and we look forward to working with ICER to accurately and collaboratively assess the values of orphan therapies. For questions regarding NORD or the above comments, please contact me at rsheer@rarediseases.org, or 202-588-5700.

Thank you in advance for your consideration.

Sincerely,

/s/

Rachel Sher
Vice President of Policy and Regulatory Affairs



251 18th Street South
Suite 630
Arlington, VA 22202
800-231-4222: tel
www.nof.org

June 10, 2019

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

Submitted Electronically: publiccomments@icer-review.org

RE: 2020 Update to ICER Value Framework

Dear Dr. Pearson,

The National Osteoporosis Foundation (NOF) is pleased to respond to the Institute for Clinical and Economic Review's (ICER's) call for stakeholder comments to inform its value framework update. Our comments reflect our interest in engaging ICER in a continuing dialogue to ensure that patients with osteoporosis receive clinically appropriate treatments to manage this chronic disease.

NOF is the nation's leading resource for patients, health care professionals and organizations seeking up-to-date, medically sound information and program materials on the causes, prevention and treatment of osteoporosis. Established in 1984 as America's only voluntary, nonprofit health organization dedicated to reducing the widespread prevalence of osteoporosis, the foundation has grown to include a network of diverse stakeholders that support its goals to increase public awareness and knowledge, educate physicians and health care professionals, and support research activities concerning osteoporosis and related areas.

Our Policy Institute brings together the expertise, resources, and perspective of the full spectrum of bone health stakeholders to advocate for health policy initiatives that promote bone health and reduce both the personal and financial costs of fragility fractures. Included in NOF's core mission are efforts to stimulate education and research toward advancing appropriate use of existing therapies and development of new treatment options.

NOF leadership and colleagues representing the National Bone Health Alliance (NBHA) provided input and shared our concerns with ICER, both within the comment processes and at the California Technology Assessment Forum (CTAF) public meeting assessing the comparative clinical effectiveness and value of anabolic agents (teriparatide and abaloparatide) for the treatment of osteoporosis in postmenopausal women.



251 18th Street South
Suite 630
Arlington, VA 22202
800-231-4222: tel
www.nof.org

We support ICER's goal of improving the quantity and quality of information available to clinicians, patients, and payers so that treatment and coverage decisions lead to high-value health care for all Americans. ICER has recognized that osteoporosis is an emerging health policy crisis that threatens to further stress our health care financing systems.

Osteoporosis, the weakening of the bones through loss of bone mineral content and a decrease in bone quality, is a common disease of aging that affects approximately 10 million Americans. Approximately half of women and one quarter of men will suffer at least one fracture due to osteoporosis during their lifetimes. Experts estimate that there are approximately two million osteoporotic fractures each year, which results in \$19 billion in related costs. By 2025, these figures are predicted to grow to approximately three million fractures and \$25 billion in costs annually as the population of older Americans increases.¹

Although new diagnostic and treatment options continue to emerge, osteoporosis remains under-diagnosed and under-treated. The care gap in osteoporosis has actually worsened over time. It is, therefore, critical that physicians and patients have access to important new therapies to determine the best course of treatment for each individual. In fact, in a recent NOF survey of 2,200+ patients and caregivers, 98 percent stressed the importance of access to all available osteoporosis treatments. Of this same patient population, 43% had been prescribed two or more osteoporosis medications throughout their treatment, underscoring the unique circumstances for many osteoporosis patients whose fracture risk and type of treatment may change over time.

Our comments reflect our hope that ICER's framework update will drive recognition of the inherent value in, and cost-effectiveness of, addressing the osteoporosis care gap and reducing the prevalence of preventable fragility fractures.

ICER should ensure that its assumptions on disease burden, costs of care, and incremental cost of new treatments are up to date.

Accurate estimates of the base case costs associated with a particular condition are an essential component of a valid health economic review. ICER's preference for robust data, collected over a long time period may, unfortunately, may have the unintended consequence of skewing cost estimates and reducing assessment reliability. Osteoporosis offers a clear example of ICER's methodology driving underestimates in care costs associated with fragility fractures. The model most recently used included cost inputs from 30 years ago. While ICER adjusted historic cost estimates for inflation, that adjustment did not account for the changes in care and the use of new technology that has occurred in the last 25 years. The resulting adjusted inputs underestimate the financial burden of osteoporosis by as much as 50% when compared to estimates generated from

¹ <https://icer-review.org/topic/osteoporosis/>



251 18th Street South
Suite 630
Arlington, VA 22202
800-231-4222: tel
www.nof.org

2007-14 care data. Similarly, we ask that ICER recognize the long-term consequences of fragility fractures on patients and account for disease burden beyond the acute care and rehabilitation settings to capture longer-term impact on mortality and morbidity.

Underestimating the burden of osteoporosis ultimately reduces ICER's calculated value for treatments it reviews despite their demonstrated efficacy in preventing fractures. Given that the treatment rates for elderly post-fracture patients at greatest risk of a fragility fracture are as low as 20%, ICER should ensure that its evaluations do not perpetuate under treatment by under-valuing new treatment options.

ICER should incorporate disease-specific, real world patient experience and preferences into its quantitative value assessments.

ICER has expressed a commitment to incorporating the patient experience into its reviews and has published final reports on new products that include patient preference information within a discussion of contextual considerations. We urge ICER to incorporate relevant real-world data and patient preference information into the assumptions and other inputs that ultimately drive its efforts to quantify value. This is especially important within the context of osteoporosis treatments and other conditions with high rates of under-treatment and treatment discontinuation.

- ICER assumes 100% persistence for existing treatments in its base case despite peer-reviewed publications suggesting real world discontinuation rates of 30-60%;
- ICER's osteoporosis model compared therapies of different duration and extrapolated efficacy estimates without adjusting for persistence;
- ICER selected zoledronic acid (ZA) as the comparator against which newer bone-forming agents would be reviewed despite the fact that these agents slow bone loss rather than build new bone, and are generally used in a treatment context that differs from the reviewed bone-forming agents;

We urge ICER to:

- Compare treatments that have similar impacts on the underlying disease process;
- Take into account that higher-risk patients may require more rapid-impact treatments;
- Simulate real world estimates of persistence of each therapy over time; and
- Assume credible ranges for the decline of effect over time.

NOF believes that ICER's review process may be better-equipped to address existing shortcomings on model inputs and assumptions if ICER provided sufficiently generous comment timeframes to enable stakeholders to prepare meaningful responses. Accuracy, validity, and completeness should take priority over the expedience of established timelines, particularly when patients have their health, and even their lives at stake.



251 18th Street South
Suite 630
Arlington, VA 22202
800-231-4222: tel
www.nof.org

ICER should increase its patient and caregiver community engagement efforts throughout its process

ICER's most recent review of osteoporosis treatments acknowledged the inherent difficulties in ensuring that value is assessed in a patient-centric manner. Those difficulties cannot be overcome, however, unless patient and caregiver engagement are at the center of ICER's assessments and meaningfully inform its understanding of the outcomes that are relevant to patients.

NOF has recently reached out to the patient and caregiver community to explore the preferences that drive treatment decisions and persistence, including the all-too-frequent decision to decline treatment or diagnostic testing. Patient advocacy organizations across disease states have recognized the importance of the patient voice throughout the product development and approval processes. This important information should also play a pivotal role in any evaluations that, like ICER's work, are intended to or could have the effect of shaping access. Outcomes specific to patients and their disease state, such as alleviation of symptoms or the ability to be productive in work or home settings, often are not captured through clinical trial data or reflected by global or specific clinical measures that feed into a QALY. Patient advocates, armed with sufficient time to devise proactive and meaningful input, can not only improve the validity of ICER's assessments, but increase patient acceptance of and agreement on the results of its reviews.

We urge ICER to ensure that patient organizations have sufficient advance notice of an upcoming review to gather data on outcomes most important to patients, disease burden, and factors that might encourage or discourage patients considering a treatment, and that this information is appropriately incorporated into ICER's reports. We also believe that ICER's practice of limiting stakeholder input to a 10-page maximum dilutes its message of inclusiveness and collaboration with patients and their advocacy organizations.

ICER's analyses should consider the disease-specific patient population.

NOF has previously expressed our concern that complicated patients with osteoporosis -- patients who are excluded from randomized clinical trials -- are not adequately considered in ICER's reports. While we understand ICER's strong preference for relying on the highest level of evidence, patients at highest risk for fracture may not be captured in that evidence. For these patients, using and even starting with a newer therapy may sometimes be the best choice. ICER does a serious disservice to these patients if it discounts the validity of the as-yet-unpublished clinical trial data and substantial observational data on this subpopulation into its evaluation.



251 18th Street South
Suite 630
Arlington, VA 22202
800-231-4222: tel
www.nof.org

Similarly, ICER's use of Net Health Benefit ignores the urgency to treat in some patients. Patients who have had a prior fracture and those with multiple fractures have a substantially increased risk for future fracture, particularly within the 2-year period following the initial fracture. ICER reviews should not ignore the added benefit of faster action in addressing low bone density for individuals at greatest near-term risk of fragility fracture.

Conclusion

Once again, NOF appreciates the opportunity to provide feedback as ICER considers updates to its value framework. We look forward to working with you to ensure that patients with bone fragility receive the treatment they need to avoid preventable fragility fractures and improve their overall health outcomes.

If you have any questions or wish to discuss our concerns in greater detail, please contact me at 703-647-3020 or our Chief Mission Officer, Claire Gill, at 703-647-3025.

Very truly yours,

A handwritten signature in black ink, appearing to read 'Elizabeth Thompson', with a long, sweeping horizontal line extending to the right.

Elizabeth Thompson
Chief Executive Officer
National Osteoporosis Foundation

June 10, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Public Input for 2020 Value Assessment Framework

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson:

The National Pharmaceutical Council (NPC) shares your interest in translating “evidence into policy decisions that lead to a more effective, efficient, and just health care system.”¹ NPC launched the *Going Below the Surface* initiative² with this view in mind. NPC appreciates ICER’s call for public input for the 2020 Value Assessment Framework.³

NPC is a health policy research organization dedicated to the advancement of good evidence and science, and to fostering an environment in the United States that supports medical innovation. NPC is supported by the major U.S. research-based biopharmaceutical companies. We focus on research development, information dissemination, education and communication of the critical issues of evidence, innovation and the value of medicines for patients. Our research helps inform critical health care policy debates and supports the achievement of the best patient outcomes in the most efficient way possible.

As stated in NPC’s *Guiding Practices for Patient-Centered Value Assessment (Guiding Practices)*,⁴ and in our prior comments on the ICER Value Assessment Framework,^{5,6} we believe value assessments can be an important tool for the complex decisions organizations and patients face when considering treatment options. Assessments that adhere to the *Guiding Practices* can support optimal value for patients.

ICER’s prior framework revisions⁷ made changes that created greater alignment with the *Guiding Practices*, and we look forward to seeing even greater alignment with the 2020 revision. There are three broad areas of improvement that are needed:

- improvements to the **framework** itself,
- improvements to the assessment **process**, and
- an **expanded focus** to include the entire health care system.

Detailed suggestions for improvement in these three areas are presented below.

I. Improvements to the Framework

NPC recommends improvements to eight areas of the ICER Value Assessment Framework:

- Include societal perspective as a base case
- Use a collaborative model to achieve a realistic base case
- Increase subgroup analyses
- Include real-world evidence
- Quantitatively integrate additional benefits / contextual considerations
- Lay the groundwork to replace or augment cost-per-QALY based methodology
- Leave budget impact assessment to the end user
- Eliminate assessment of affordability and use of artificial affordability threshold

The motivation for each of these recommendations is presented below.

A. Include Societal Perspective as a Base Case

NPC's prior comments recommended the use of a "societal perspective" for ICER's cost-effectiveness analyses (CEA). This recommendation is echoed in the recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine (Second Panel), which emphasizes the importance of the societal perspective as at least one of the base cases for CEA.⁸ Guiding Practice VIII emphasizes the importance of utilizing methods based on established health economic methodologies, such as the those of the Second Panel.

The societal perspective can incorporate important factors such as productivity and caregiver burden. A societal perspective will ensure that all patient- and societal-focused benefits are included, not just those that will be accrued by the payer.

NPC recommends that ICER include the societal perspective as a co-base case in all reviews and include the results from the societal perspective base case in all result summaries such as press releases and report-at-a-glance documents.

B. Use a Collaborative Model to Achieve a Realistic Base Case

The *Guiding Practices* underscore the importance of ensuring that the foundation for all assessment results, the base case, is realistic (Guiding Practice X). NPC's members have pointed to some examples of contested base case assumptions from individual reviews:

- **Population.** ICER may choose the entire population in its models rather than the target population identified in the label. At launch, data are only available for the target population. Additionally, the expanded population leads to an artificially high estimate of budget impact.
- **Comparator.** ICER may choose a placebo comparator rather than a more realistic real-world comparator. Focusing on a placebo often leads to an inflated estimate of the incremental cost per quality adjusted life year (QALY).

- **Model.** In the rheumatoid arthritis review, ICER chose to use a Markov model, while the majority of recently published models, including NICE's model, used an individual patient simulation (IPS) approach. The Markov model led to significantly different results.

Achieving a realistic base case can be aided by a collaborative and transparent model development process, such as the one used by the Advisory Committee on Immunization Practices (ACIP).⁹ In the ACIP process, a manufacturer's model can be presented at the public meeting alongside an ACIP model. A collaborative process that explores different base cases can promote consensus on realistic base case assumptions.

NPC recommends that ICER pilot a collaborative and transparent model development process like the ACIP process that allows for a manufacturer's model to be presented alongside ICER's model, highlighting differences in the base case assumptions or modeling approach.

C. Increase Subgroup Analyses

Guiding Practice XIV speaks to the importance of recognizing that patients are heterogeneous and respond to treatments differently. Subgroup and scenario analyses should be built into the assessment process to capture this heterogeneity, including the estimation of value-based prices for the various analyses. Reporting a single value-based price for the average patient implies a false sense of precision and generalizability to the end-user. To avoid this false impression, the full range of estimated value-based prices should be reported in result summaries. Subgroup analysis should not be performed if sample size is inadequate, however.

NPC recommends that ICER include more subgroup and scenario analyses in its assessments. Value-based prices should be estimated for these analyses, and the full range of value-based prices should be included in result summaries such as press releases and report-at-a-glance documents.

D. Include Real-World Evidence

Guiding Practice XXII emphasizes that assessments should use the best available evidence. ICER's assessments rely heavily on evidence from traditional randomized clinical trials (RCTs). Traditional RCTs are designed to answer whether a treatment can work and are not designed to answer whether treatments work in real-world populations and settings. Real-world patient data can be better suited to inform payer decision making and answer for whom the treatment works.

The evidence landscape is evolving due to higher quality real-world data sources, improved curation and analytic methods, and broader use of real-world evidence (RWE). With the growing focus on personalized medicine, smaller patient populations make RCTs harder and more expensive to conduct.

Recently, in response to provisions of the 21st Century Cures Act, the Food and Drug Administration (FDA) released the *Framework for FDA's Real-World Evidence Program* as a

guide for how to evaluate RWE as a way to “complement, augment and expand our understanding of how best to use medical products—improving what we know about our medical care.”¹⁰ Just as the FDA is evolving in their use of real-world data, we encourage ICER to adopt a similar stance on broader use of real-world evidence and data, not only relying on these alternative evidence sources when high-quality RCTs are not available, or pre-emptively limiting the study type when determining study inclusion and exclusion criteria based on blunt estimates of study quality such as sample size.

NPC recognizes that RWE will not be available for many new drugs at launch, but it is often available for products that have been on the market for a while and can be useful for therapeutic area class reviews or for updated reviews. This RWE evidence can be used to improve the evidence base in ICER’s assessments. For example, a high quality prospective observational study could bridge the gap in long-term, consistent RCT evidence.

Finally, improved methods to incorporate observational studies in the ICER Evidence Rating Matrix are needed. As described in the ICER Evidence Rating Matrix: A User’s Guide case study describing leukotriene inhibitors, decision-makers would make a different comparative clinical effectiveness rating if the evidence synthesis relied solely on RCTs rather than the totality of the evidence.¹¹ Limited consideration of RWE studies can alter not only the magnitude of the net health benefit, but also the level of evidence certainty when RWE studies complement rather than compete with RCTs.

NPC recommends that ICER increase the use of real-world evidence in its assessments for all outcomes, utilize existing good standards for evaluation of real-world evidence, and enhance the integration of real-world evidence in evidence synthesis and rating.

E. Quantitatively Integrate Additional Benefits / Contextual Considerations

Guiding Practice XIII states that “measurement of value should include a broad array of benefits that are important to patients and society.” While ICER seeks to identify these benefits, they are merely listed in the reports as ‘Additional Considerations.’ They are not measured or formally incorporated into the assessment results.

ICER’s current approach leaves the consideration of these factors up to the discretion of the voting panel, which may not have the expertise or appropriate context to meaningfully evaluate them. Moreover, this valuation approach that is heavily dependent upon the perspectives and decisions of a small group, is not transparent or consistent. This approach is insufficient to incorporate the impact of these important patient-centered factors.

NPC recognizes that there is no gold standard methodology for quantitatively incorporating these factors into assessment results. However, it is critical that these methodologies, such as multiple-criteria decision analysis (MCDA), be developed and tested.

NPC recommends that ICER partner with researchers at organizations such as Center for Enhanced Value Assessment (CEVA), Pharmaceutical Value (pValue), and the Innovation and Value Initiative (IVI) to lead the way towards the piloting of a consistent and transparent methodology to quantitatively incorporate these important factors in ICER’s value assessments.

F. Lay the Groundwork to Replace or Augment Cost-Per-QALY Based Methodology

As detailed in NPC's prior comments, use of the QALY poses several significant concerns, primarily ethical considerations, methodologic issues and disease-specific considerations.¹² ICER itself has identified key problems with the QALY.¹³ These concerns serve to heighten the importance of the development and testing of alternative value assessment methodologies to replace or augment ICER's current approach, as addressed in the preceding section.

If the QALY is used (despite the limitations noted above), it should be recognized that no single cost-per-QALY threshold can or should be universally applicable, as thresholds are likely to vary by decision-maker, population, and disease. Neumann, Cohen, and Weinstein state:

...it is impossible to find a single threshold to represent society's willingness to pay for QALYs gained, because different approaches yield different values, each of which is based on different assumptions, inferences, and contexts. Searching for a single benchmark is at best a quixotic exercise because there is no threshold that is appropriate in all decision contexts.¹⁴

Evidence exists that willingness to pay for life-saving conditions is more than that for minor conditions,¹⁵ and even higher for rare and ultra-orphan disease. Under its "highly specialised technology" process, the National Institute for Health and Care Excellence (NICE) proposes to use cost-per-QALY thresholds for ultra-orphan diseases that are 5-10 times its standard level.¹⁶ Willingness to pay for oncology suggests thresholds that are much higher than what ICER currently uses as an upper bound.^{17,18} Some real-world coverage decisions in the U.S. are similarly consistent with higher WTP thresholds. These signals of potentially higher thresholds in the U.S. should not be ignored, especially given the absence of a multi-stakeholder evaluation process to determine true societal WTP in the U.S.

The reality is that we do not know what society's willingness to pay (WTP) is in the U.S. for various diseases and scenarios. Guiding Practice XIX recommends a multi-stakeholder evaluation process reflecting societal values be used to set specific thresholds, and this has not occurred.

NPC recommends that this uncertainty about U.S. WTP for various diseases and scenarios be addressed in the short run by using higher upper bound cost-per-QALY thresholds, and in the long run by developing and testing alternative value assessment methodologies to replace or augment the cost-per-QALY based methodology.

G. Leave Budget Impact Assessment to the End User

Budget Impact Guiding Practice II states that "budget impact assessments should be separate from value assessments." Budget impact assessment (BIA) is a measure of resource use, not a measure of value, and it has no role in value assessment.

NPC recognizes that budget impact is an important construct for individual payers in their decision-making process. Payers should estimate budget impact for their own populations.

ICER's estimates of national budget impact are not relevant to these payers or useful for their decision-making purposes.

NPC recommends that ICER's value assessments should focus solely on value. The estimation of national budget impact should be eliminated from assessments, leaving budget impact estimation to the end user.

H. Eliminate Assessment of Affordability and Use of Artificial Affordability Threshold

Budget Impact Guiding Practice VI says that “a BIA is simply an assessment of budget impact, and should not be judged against artificial affordability caps.” Affordability is an important concept for society. Evaluating affordability involves making assessments and trade-offs at an overall health system level (i.e., a broad assessment of all investments in a health care system) and beyond the health system (i.e., spending on health care versus other societal considerations, such as education, police, and roads).

A comprehensive approach to affordability requires considerations of concepts such as disinvestment and tradeoffs, needs to be informed by cultural and societal values as well as health and non-health needs, and requires broad stakeholder involvement. ICER's current approach to assessing affordability—setting a potential budget impact threshold that may trigger an “affordability alert”—is not a comprehensive consideration of the health care system, does not consider societal values, and does not adequately measure affordability.

Not only would an affordability assessment require decisions about health care spending versus non-health care spending, it also would require societal decisions about intra-health care spending. This would force decision-makers to make trade-offs regarding spending on the elderly versus the young, rare disorders versus common diseases, and curative therapies versus prolonging life or quality-of-life enhancement, as well as allocations among medications, surgery, hospital care, and physician services.

ICER's current approach of setting a uniform budget impact threshold based on a fixed portion of drug expenditures creates an artificial affordability threshold that could have negative, unintended consequences. An analysis by IQVIA (formerly IMS) and NPC demonstrates that ICER's affordability threshold could lead to an inefficient allocation of health care resources.¹⁹ If the affordability threshold—which is not based on value—causes us to shift this spending away from high-value drugs, it could be shifting money toward lower-value care that is less efficient, paradoxically reducing the value of our health care dollar.

Another unintended consequence of an artificial affordability threshold is the disincentivization of the development of drugs for broad populations with unmet need. Predicted budget impact will increase as the predicted number of patients increases, causing a treatment for a broad population—particularly one with unmet need—to be more likely to trigger an “affordability alert” threshold. However, a comprehensive affordability assessment that considers societal values and the broader public health perspective would likely result in a higher spending allocation for such a treatment.

Finally, the ICER threshold equation assumes that the allocation of health care spending among drugs, hospital care, imaging and physician care is the “correct” allocation across resources. For example, perhaps more resources should be spent on drugs and less on imaging for optimal resource allocation, or vice versa. The derived threshold assumes that the current allocation is optimal, an unproven assumption that is likely incorrect.

NPC recommends that ICER eliminate its assessment of affordability as well as its use of an artificial affordability threshold.

II. Improvements to the Assessment Process

NPC recommends improvements to four areas of the ICER Value Assessment Process:

- Include broader results in press releases and report-at-a-glance documents
- Enable full transparency and reproducibility by making the ICER model publicly available
- Extend length of time for review
- Establish a disease-specific working group of clinicians for each assessment

More details about these recommendations are presented below.

A. Include Broader Results in Press Releases and Report-at-a-Glance Documents

As noted above in section I.C., reporting a single value-based price (VBP) for the average patient implies a false sense of precision to the end-user. Although ICER’s VBP results appear to have a range, this range relates solely to the use of different thresholds. For any given threshold, however, there is the implication that the VBP point estimate is accurate. There is uncertainty around this estimate due to uncertainty in the data and model assumptions, and ICER should provide ranges around each of these point estimates to indicate this uncertainty.

This uncertainty extends beyond the VBP estimates for the base case. There are different estimates for each analysis beyond the base case, such as those with different subgroups, different scenarios, and different perspectives (such as the societal perspective in section I.A.). The VBP estimates and confidence intervals for these additional analyses should be reported in result summaries so the full extent of uncertainty is recognized by the end user.

NPC recommends that ICER include broader results in summaries such as press releases and report-at-a-glance documents. These results should include the societal perspective as a co-base case and a full range of potential value-based prices, and the confidence intervals around these prices.

B. Enable Full Transparency and Reproducibility by Making the ICER Model Publicly Available

Guiding Practice IX emphasizes that transparency and reproducibility are necessary for demonstrating credibility and validity of assessments. NPC's prior comments have highlighted the lack of transparency and reproducibility inherent in ICER's models.

NPC commends ICER for introducing a pilot program to share models with manufacturers in 2018.²⁰ While this was a clear step in the right direction, we agree with the limitations to ICER's approach that have been noted by others: models should be available to all stakeholders rather than subject to restricted access; models should be fully available for use and customization rather than only available for review; and model sharing should not include confidentiality agreements that restrict the ability to share and discuss the models freely with all stakeholders.²¹ We also recommend conducting live Q&A sessions to discuss the assessment model, where stakeholders can ask clarifying questions to the model developers until the model is explained to the extent that allows accurate reproduction.

NPC strongly recommends and underscores the need for full access and transparency—down to the equation level—to enable reproducible results and support fully informed stakeholder collaboration.

C. Extend Length of Time for Review

Guiding Practice IV notes that public comment periods need to be long enough to allow for comprehensive review of materials and submission of comments. NPC acknowledges that ICER has previously extended the time for stakeholders to submit comments on scoping documents and reports, but the amount of time is still far too short for most stakeholders and is inconsistent with timelines used by other HTA bodies and the government.

Patient groups have reported difficulty with reviewing assessment reports, identifying key issues and concerns, and developing constructive comments in such a limited amount of time. Greater effort needs to be made to meaningfully elicit the patient's voice proactively and throughout the assessment process.

NPC recommends that additional time should be included for meaningful review and feedback by all interested stakeholders.

D. Establish a Disease-Specific Working Group of Clinicians for Each Assessment

Individual reviews are lacking in guidance from sufficient disease-specific clinical expertise. This could be addressed by mirroring the ACIP process noted above in I.B. For each drug evaluation, ICER could convene a working group of 8-12 clinicians with expertise in the disease or therapeutic area under review. This working group would provide clinical guidance on the selection of comparators, model parameters, and evidence to include or exclude, and they would benefit from seeing both ICER and industry models as they make these decisions. Since these

choices are critical to the final assessment results, having a working group of clinical experts to provide direction will improve the credibility and accuracy of the results.

NPC recommends that ICER convene a working group of clinicians with disease-specific expertise for each review. Similar to the ACIP process, this working group would see both ICER and industry models and provide direction on important choices such as selection of comparators, model parameters, and evidence base.

III. Expanded Focus on the Entire Health Care System

Guiding Practice VII states that “value assessments should focus broadly on all aspects of the health care system, not just on medications.” This point is critical to the achievement of ICER and NPC’s shared goal, noted in this letter’s first sentence: a more effective, efficient, and just health care system. Drug spending accounts for only 16% of the U.S. health care dollar.²² To truly achieve a more just, more efficient, and more effective health care system, value assessments must consider the other 84%, too. Since drugs represent a limited portion of the overall health care budget, ICER’s impact on the health care system would increase if its agenda was less concentrated and considered other interventions.

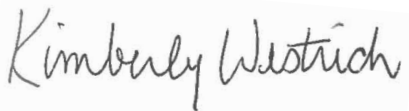
NPC recommends that ICER expand the focus of its assessments to the entire health system and conduct a proportionate share of value assessments for other parts of the health care system.

We appreciate this opportunity to provide input on potential changes to ICER’s 2020 Value Assessment Framework. NPC’s continued engagement with ICER signifies our commitment to the critical dialogue necessary to ensure the development of high-quality, meaningful value assessment tools that help patients, physicians, payers, and others make informed decisions about all aspects of their health care treatments and services.

Respectfully submitted,



Robert W. Dubois, MD, PhD
Chief Science Officer



Kimberly Westrich, MA
Vice President, Health Services Research

References

- ¹ About ICER. <https://icer-review.org/about/>. Institute for Clinical and Economic Review. Accessed May 3, 2019.
- ² Going Below the Surface. <https://www.goingbelowthesurface.org/>. Going Below the Surface. Accessed May 27, 2019.
- ³ ICER Seeks Public Input for 2020 Value Assessment Framework. Institute for Clinical and Economic Review. <https://icer-review.org/announcements/icer-seeks-public-input-for-2020-value-assessment-framework/>. May 2, 2019. Accessed May 3, 2019.
- ⁴ Guiding Practices for Patient-Centered Value Assessment. National Pharmaceutical Council. <http://www.npcnow.org/sites/default/files/npc-guiding-practices-for-patient-centered-value-assessment.pdf>. Accessed May 3, 2019.
- ⁵ NPC Comments on Proposed Improvements to ICER's Value Assessment Framework. National Pharmaceutical Council. <http://www.npcnow.org/sites/default/files/160909npc-comments-ICER-value-framework-final.pdf>. September 12, 2019. Accessed May 3, 2019.
- ⁶ NPC Comments on Proposed Updates to ICER's Value Assessment Framework. National Pharmaceutical Council. <https://www.npcnow.org/newsroom/commentary/npc-comments-proposed-updates-icers-value-assessment-framework>. Accessed May 3, 2019.
- ⁷ Overview of the ICER value assessment framework and update for 2017-2019. Institute for Clinical and Economic Review. <http://icer-review.org/wp-content/uploads/2017/06/ICER-value-assessment-framework-Updated-050818.pdf>. Accessed May 26, 2019.
- ⁸ Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses. *JAMA*. 2016;316():1093-1103. doi:10.1001/jama.2016.12195.
- ⁹ Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention. <https://www.cdc.gov/vaccines/acip/index.html>. Accessed May 27, 2019.
- ¹⁰ Framework for FDA's Real-World Evidence Program. U.S. Food & Drug Administration. <https://www.fda.gov/media/120060/download>. December 2018. Accessed June 6, 2019.
- ¹¹ ICER Evidence Rating Matrix: A User's Guide. <http://icer-review.org/wp-content/uploads/2016/02/Rating-Matrix-User-Guide-UPDATED-06.30.17.pdf>. Institute for Clinical and Economic Review. July 18, 2017. Accessed June 5, 2019.
- ¹² Pettitt DA, Raza S, Naughton B, et al. The Limitations of QALY: A Literature Review. *J Stem Cell Res Ther*. 2016;6(4) 1-7. <http://www.omicsonline.org/open-access/the-limitations-of-qaly-a-literature-review-2157-7633-1000334.pdf>. Accessed May 26, 2019.

- ¹³ Pearson SD. A Framework to Guide Payer Assessment of the Value of Medical Treatments. Institute for Clinical and Economic Review. <http://icer-review.org/wp-content/uploads/2014/01/Value-Assessment-Framework-DRAFT-6-13-14.pdf>. June 12, 2014. Accessed May 26, 2019.
- ¹⁴ Neumann PJ, Cohen JT, Weinstein MC. Updating Cost-Effectiveness — The Curious Resilience of the \$50,000-per-QALY Threshold. *N Engl J Med* 2014;371:796-797. doi: 10.1056/NEJMp1405158.
- ¹⁵ Gross SD. Assessing Cost-Effectiveness in Healthcare: History of the \$50,000 per QALY Threshold. *Expert Rev. Pharmacoeconomics Outcomes Res.* 2008;8(2), 165-178.
- ¹⁶ Raftery J. NICE's proposed new QALY modifier for appraising highly specialised technologies *The BMJ Opinion*. <http://blogs.bmj.com/bmj/2017/04/18/nices-proposed-new-qaly-modifier-for-appraising-highly-specialised-technologies/>. April 17, 2018. Accessed June 6, 2019.
- ¹⁷ Nadler E, Eckert B, Neumann P. Do Oncologists Believe New Cancer Drugs Offer Good Value? *The Oncologist*. 2006 Feb;11(2):90-5. doi: 10.1634/theoncologist.11-2-90.
- ¹⁸ Seabury SA, Goldman DP, Maclean JR, et al. Patients Value Metastatic Cancer Therapy More Highly Than Is Typically Shown Through Traditional Estimates *Health Affairs*. 2012 Apr;31(4):691-699.
- ¹⁹ Ciarametaro M, Abedi S, Sohn A, Fan Ge C, Odedara N, Dubois RW. Concerns around budget impact thresholds: not all drugs are the same. *Value in Health*. 2017 Feb;20(2):230-233. doi: 10.1016/j.jval.2016.11.031.
- ²⁰ Institute for Clinical and Economic Review Announces New Program to Make Available Draft Executable Economic Models During Drug Assessment Review Process. Institute for Clinical and Economic Review. <http://icer-review.org/announcements/model-transparency-program>. March 30, 2018. Accessed May 26, 2019.
- ²¹ IVI responds to ICER's new pilot program. Innovation and Value Initiative. <http://www.thevalueinitiative.org/ivi-responds-to-icers-new-pilot-program>. April 3, 2018. Accessed May 26, 2019.
- ²² Kleinrock M, et al. Reconciling the Seemingly Irreconcilable: How Much Are We Spending on Drugs? *Value in Health*. [https://www.valueinhealthjournal.com/article/S1098-3015\(18\)36310-1/fulltext](https://www.valueinhealthjournal.com/article/S1098-3015(18)36310-1/fulltext). January 11, 2019, online ahead of print. Accessed May 26, 2019.

Novartis Response: ICER 2017 Value Framework (June 10, 2019)

Primary Contact:

Vivian Herrera, MPH, MIA, DDS

Vice President, Head US HE&OR

US Health Economics & Outcomes Research and Medical Access

Novartis Pharmaceuticals Corporation

E-mail: vivian-1.herrera@novartis.com

Novartis appreciates the opportunity to provide feedback on the Proposed Improvements to ICER's Value Assessment Framework. Based on our experience engaging in the evaluation process on a number of ICER reviews as well as a detailed review of ICER's 2017 value framework, we recommend the following considerations be taken into account when developing the Value Assessment Framework for 2020 and beyond. We hope to see updates that address the need for:

1. Dynamic cost-effectiveness thresholds;
2. Higher cost-effectiveness thresholds in supported contexts;
3. Life-cycle drug costs;
4. Comprehensive budget impact analysis;
5. Supplementing randomized controlled trial evidence with real world evidence;
6. Use of Multi Criteria Decision Analysis;
7. Inclusion of contextual considerations in the calculation of value;
8. Formally structured input from patient and patient advocate organizations;
9. Adequate inclusion of expert opinion; *and*
10. Increased transparency of ICER's models.

Specifically, we recommend the following changes for the next value assessment framework.

1. Capture Dynamic Disease Circumstances in Cost-Effectiveness Thresholds

- The ICER cost-effectiveness thresholds of \$50,000, \$100,000, and \$150,000 are used as benchmarks for whether products are low, intermediate, or high value. They are also used to calculate value-based price benchmarks, which are frequently the topline result published in the ICER press released and picked up by the media. However, these thresholds have been, and remain controversial.
- The appropriateness of the cost-effectiveness thresholds have been questioned, particularly for rare disease, oncologic treatments, and chronic diseases.¹ The selection of these cost-effectiveness thresholds are critically important as a low/high value findings have disproportionate impacts on coverage and access decisions. The perception in the marketplace suggests that a low value finding may have a bigger (negative) impact than a high value finding would have on gaining coverage. As a result, the selection of the upper threshold is quite critical.
- We recommend changing the cost-effectiveness thresholds to be dynamic for each evaluation, taking into account how adoption (and enforcement) of a higher threshold for defining cost-effectiveness affects current health care spending and alters spending over time.¹ One approach to selecting a threshold is based on preferences from the general public and the value they attach to health improvements.² These preferences may change over time, based on changing technology and shifting priorities. Additionally, thresholds should be refined on a regular basis to account for inflation, and changes in per capita income, innovation in diagnosis and treatment, burden of disease, and patient preferences.¹

2. Consider Use of Higher Cost-Effectiveness Threshold

- ICER should incorporate alternative cost-effectiveness thresholds for disease areas with evidence of a higher willingness-to-pay. There is substantial evidence of society having a flexible perspective on an acceptable cost-effectiveness threshold. Evidence in the literature suggests that society may be willing to pay more than the usual \$50,000-\$150,000 per QALY for younger patients including children and patients with more severe disease; and that we should not be only looking at willingness-to-pay (WTP) in terms of fixed QALY thresholds.³
- The literature demonstrates that there is variation in what might be considered to be a reasonable cost per QALY, and the range of estimates is broad. Given the importance of the upper limit because of the implications of a low value finding on coverage, and the wide variation at the upper limit of estimates of a QALY, it would be reasonable for ICER to consider a higher upper threshold.
 - Since 2006, the Food and Drug Administration (FDA) has utilized cost-benefit analyses in some of its important rulemakings. In these cases, QALYs were converted to dollars using a conversion factor that ranged from \$100,000-\$500,000; the dollar amounts were then inputted to a monetized cost-benefit analysis.⁴
 - A 2007 report prepared by the Lewin Group, under contract to the Assistant Secretary for Planning and Evaluation (part of the U.S. Department of Health and Human Services), stated that a 2002 review article suggested that the cost-utility ratio for health-related screening methods introduced and widely utilized from 1993-2000 was approximately \$500,000 per QALY.^{5,6}
 - Lee et al. (Value in Health 2009) evaluated the cost-effectiveness of dialysis versus the next least costly alternative to determine how the incremental cost-effectiveness ratio differs based on variations in practice patterns and within patient subgroups. The incremental cost-effectiveness ratio was on average \$129,090 per quality-adjusted life-year (QALY), the interquartile range was \$71,890 per QALY, and the 1st and 99th percentiles were \$65,496 and \$488,360 per QALY, respectively.⁷

3. Model Life-Cycle Drug Costs

- In its last value framework update, ICER moved for using WAC list prices to net prices calculated in partnership with SSR Health. We would recommend ICER taking the next step forward and include a standard sensitivity analysis that estimates cost-effectiveness accounting for the loss of exclusivity (LOE) when the patent on a treatment expires. The loss of exclusivity (LOE) of a medication affects the price of the treatment with that therapy. As competitors and generic options emerge, the cost of treatment significantly declines. An accurate reflection of real-world prices is a necessary component of a cost-effectiveness analysis. The inclusion of stakeholder evidence of price declines would ensure relevant and accurate pricing in future models, and result in more unbiased reporting of the cost-effectiveness and budget impact aspects of a medication.

4. Perform a Comprehensive Budget Impact Analysis

- ICER should consider a larger range of outcomes when projecting budget impact. Budget impact analyses from ICER have historically not reflected realized costs. One

concern that arises from this trend is the possibility that payers have limited access to medications that have been projected to have costly impacts. A consequence of this scenario is the restricted opportunity to treat patients with a medication that offered them a superior risk/benefit over other treatment options.

- Ultimately ICER's consideration of short-term budget impacts should be complemented with an analysis of medium- and long-term budget impacts. Premiums paid in the short-term can precipitate longer-term benefits, resulting in a medication having a cost-saving impact over the lifetime of its usage. After initial concerns over the price of hepatitis C therapies, publications are emerging that demonstrate cost-saving budget impacts.⁸⁻¹⁰ In the hepatitis C disease space, we have seen multiple health systems stakeholders working together to determine how to best provide access to care for patients, in recognition of the long-term cost-saving benefits of hepatitis C therapies.
- ICER has committed to identifying low-value therapies during its reviews. Comprehensive budget impact analysis would include the elimination of these low-value options in an attempt to offer optimal accessibility to comparatively better medications.

5. Supplement Randomized Controlled Trial (RCT) Evidence with Relevant Clinical Information from Real World Evidence (RWE)

- ICER should present sensitivity analyses to address the potential shortcomings of RCT evidence. The patient population of an RCT likely varies from a real world cohort, with a real world cohort often being sicker or evidencing greater heterogeneity in disease or treatment response.¹¹⁻¹³ This could be done by factoring in elements, such as adherence, and modeling different baseline characteristics for patients, or modeling outcomes for specific subgroups of patients to understand the variation.
- Cost-effectiveness models should be fine-tuned using RWE. While RCTs offer the strongest statistical test of a therapy's potential risks and benefits, they frequently lack an adequate representation of the patient population. Indeed, clinical trials include test subjects that are "younger, more often male, and less racially and ethnically diverse" than the realized patient population.¹⁴ RCTs also control for clinical factors such as adherence, comorbidities, concomitant treatments, study location, health system variation, and environment. RWE provides insight into the experience of individuals that deviate from these controls. The incorporation of RWE into cost-effectiveness analysis would help correct this misrepresentation and provide less biased projections of a medication's value.^{14,15}
- To improve the accuracy of the model in capturing how patients outside a clinical trial may respond, ICER should consider incorporating real world evidence in addition to clinical trial evidence. The presence of narrow patient populations in RCT evidence raises concern particularly for the evaluation of cancer-treating drugs. Off-label use, attributable costs, and patient perception of risk are additional aspects of oncology that compound uncertainty in real world outcomes.¹⁶ This increased uncertainty translates into a larger range of potential clinical and economic outcomes for oncology treatments.

6. Use Multi Criteria Decision Analysis (MCDA) to Address Limitations of the QALY

- The QALY inherently has several characteristics that make it less than ideal for comprehensively capturing all components of value. Namely, the QALY is insensitive to distribution of benefits, severity, and age. This suggests scenarios where, for example, miniscule improvements in quality of life of many people are valued the same as a significant improvement in a single individual; or, a treatment extending a terminally ill infant's life expectancy from 10 years to 20 years is valued the same as a treatment that extends an elderly person's life expectancy from 80 years to 90 years.
- Proper value definition is more likely to be achieved through a Multi Criteria Decision Analysis (MCDA) methodology and evidence-informed deliberative processes as they:
 - Use a consistent and validated set of criteria (through evidence-based analysis) to define and measure value
 - Adopt a consistent and transparent decision algorithm, which can be replicated for any technology to be assessed
 - Provide a vehicle to iteratively co-design a system with decision makers and other stakeholders that would increase the acceptability of novel medicines, allowing local adaptability.¹⁷
- MCDA is widely used in other sectors and has become a preferred method for decision analysis in many contexts.¹⁸ One example of its application is in the field of photovoltaic investments where researchers utilized a variety of MCDA known as an outranking model to decide on technologies, financial support, and business strategy.¹⁹ Given the complexity of health care decisions and inherent trade-offs between multiple often conflicting objectives, MCDA offers clarity on which criteria are relevant and the importance attached to each for value assessment.
- ICER's use of MCDA can help increase the consistency, transparency, and legitimacy of their decisions. The MCDA could be added on as an additional standard analysis after long-term value, short-term affordability, as an additional value calculator.

7. Include Contextual Considerations in Calculation of Value

- Currently contextual considerations are primarily included as a textual aside to the greater cost-effectiveness model. They are not built into the model where they would have an impact on costs or benefits and ultimately on the cost-effectiveness of the treatment itself. Given the impact of such important considerations as the effect on patient productivity or the effect on caregiver burden, among many others, a more comprehensive evaluation that explicitly incorporates these factors into the model as part of the final cost per QALY calculation is needed.
- In contrast to the suggestion that the inclusion of productivity costs in a cost-effectiveness model violates ethical considerations, inclusion of this component is necessary to produce results that reflect real world conditions and create meaningful policy. An assessment of the impact of a treatment on non-working populations can be conducted to ensure no bias against these populations is present. Models that include

productivity costs provide directly beneficial information to employer-sourced insurance plans.

- Another factor to consider is including caregiver burden, particularly for diseases affecting the very young and the very old, such as cystic fibrosis and Alzheimer's disease. A model that ignores the stress put on caregiver's productivity and health and the resulting costs creates a bias against medications that limit these costs.
- Additionally, the Value Assessment Framework should seek to capture aspects of societal value and incorporate these components into the base case analyses. Sources of societal value include: reduced uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spill-over.

8. Formally incorporate the input of patients and patient advocates

- While ICER is already interested in including patient-advocacy groups as a source of information about patient experiences and values, patient-level data could be extracted from additional sources in order to improve representation. For example, patient surveys would provide a valuable complement to input from patient advocacy groups in determining patient preferences. Such surveys have been performed in several disease areas such as melanoma, lung cancer, and atrial fibrillation.^{20,21} Real world data can assist in this goal and provide further evidence of patient preferences between treatment options.¹⁴
- As an example of a potential approach, ICER and the Multiple Sclerosis Society conducted a joint comprehensive survey during the multiple sclerosis evaluation. In addition to that type of survey, ICER should include a report-out of the findings in the evaluation report, and also look to generate quantitative output from the surveys that could help inform model parameters.
- Additionally, there should be greater inclusion of the patient voice on both the voting panel and in the outcomes captured by the evaluations. This would enable ICER to adopt a more patient driven approach, which is of interest to providers who, similar to payers, must make access decisions across a number of treatments when determining how best to providing care to their patients.
- In general, patient engagement ought to be increased during the ICER evaluation process. Following the recent National Health Council guidelines,²² patients should be considered full partners and integrated into all aspects of model development. This can be accomplished by engaging patients in every step of the model development, including pilot testing and refinement. Ample time should be built in to the process in order to achieve this goal.

9. Include expert opinion without compromising integrity

- Health technology appraisal (HTA) needs to be free from conflict of interest, yet also requires high-quality expert input. In assessments where all experts with industry relations are excluded due to concerns about conflicting motivations, the resulting

research product can be lacking. It is suggested that industry-involved experts be allowed to participate in HTAs to help ensure the quality of reports, but be excluded from voting phases, in order to protect the integrity of the decision-making process.

10. Increase the transparency of ICER models

- ICER has partnered with heRo3 to provide access to their models in a commitment to achieving greater transparency. Novartis supports ICER in this continued commitment to transparency. However, beyond that, Novartis recommends an increase in transparency in ICER documents. Currently, stakeholders are unable to replicate ICER economic models based solely on published documents, because those documents do not include extensive detail on data input, assumptions, and comparators. Increasing transparency would increase inclusiveness and buy-in from all stakeholders; however, it is not entirely clear how ICER would use the models if given access to them. Thus, there ought to be a plan or guidelines for how the full model will be assessed by ICER.
- An alternative approach would be for the ICER process to include submissions of manufacturer's product value dossiers and economic models, keeping them confidential in a manner similar to the HTA process of other countries, in the way that NICE does in the UK, for example. The goal of this approach would be to enhance dialog between different stakeholders and establish a true partnership between stakeholders and ICER. This process also has the potential to be less resource intensive for ICER.
- Thus far, ICER methodology is not transparent about the process of choosing a comparator in their evaluations. The comparator in any given study strongly influences the outcomes, and so choosing a comparator is a crucial part of the study design. To perform an accurate assessment, it is critical that ICER chooses the appropriate comparators as a benchmark. Specifically, selecting the least costly therapy as a comparator is not necessarily appropriate for cost-effectiveness evaluations. Additionally, ICER should only use comparators that are indicated for the disease condition being evaluated, particularly if the intention is to rely on clinical trial data. The full rationale for comparator selection ought to be provided for stakeholder review and input.

References

1. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? *Archives of internal medicine* 2003;163:1637-41.
2. Towse A, Pritchard C, Devlin N. Cost-effectiveness thresholds: economic and ethical issues. *Monographs* 2002.
3. A QALY is not always a QALY: The growing evidence for heterogeneity in society's value of health gains Unpublished.
4. Adler MD. QALY's and policy evaluation: a new perspective. *Yale J Health Pol'y L & Ethics* 2006;6:1.
5. The Lewin Group. Cost-effectiveness Considerations in the Approval and Adoption of New Health Technologies. 2007.
6. Yeh J, Botteman M, Pashos C, Postma M, Staginnus U. Economics of transfusion. *Transfusion Medicine and Hemotherapy* 2002;29:218-25.
7. Lee CP, Chertow GM, Zenios SA. An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. *Value in Health* 2009;12:80-7.
8. Chou JW, Silverstein AR, Goldman DP. Short-term budget affordability of hepatitis C treatments for state Medicaid programs. *BMC Health Services Research* 2019;19:140.
9. Van Nuys KB, Ronald; Chou, Jacquelyn W; Dreyfus, David; Dieterich, Douglas; Goldman, Dana P. Broad Hepatitis C Treatment Scenarios Return Substantial Health Gains, But Capacity Is A Concern. *Health Affairs* 2015;34:1666-74.
10. Leidner AJ, Chesson HW, Xu F, Ward JW, Spradling PR, Holmberg SD. Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. *Hepatology* 2015;61:1860-9.
11. Khosla S, White R, Medina J, et al. Real world evidence (RWE) - a disruptive innovation or the quiet evolution of medical evidence generation?
12. Real-World Evidence Complements Randomized Controlled Trials In Clinical Decision Making. *Health Affairs Blog*.
13. Jena AB, Chou JW, Yoon L, et al. Understanding and improving value frameworks with real-world patient outcomes. *Am J Manag Care* 2018;24:506-9.
14. Dhruva SS, Ross JS, Desai NR. Real-World Evidence: Promise and Peril For Medical Product Evaluation. *Pharmacy and Therapeutics* 2018;43:464.
15. Katkade VB, Sanders KN, Zou KH. Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. *Journal of multidisciplinary healthcare* 2018;11:295.
16. Mullins CD, Montgomery R, Tunis S. Uncertainty in assessing value of oncology treatments. *The oncologist* 2010;15:58-64.
17. Angelis A, Kanavos P. Multiple Criteria Decision Analysis (MCDA) for evaluating new medicines in Health Technology Assessment and beyond: The Advance Value Framework. *Social Science & Medicine* 2017;188:137-56.
18. Kumar A, Sah B, Singh AR, et al. A review of multi criteria decision making (MCDM) towards sustainable renewable energy development. *Renewable and Sustainable Energy Reviews* 2017;69:596-609.
19. Azzopardi B, Martinez-Cesena EA, Mutale J. Decision support system for ranking photovoltaic technologies. *IET Renewable Power Generation* 2013;7:669-79.
20. Shafrin J, Bruno A, MacEwan JP, et al. Physician and Patient Preferences for Nonvalvular Atrial Fibrillation Therapies. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2016;19:451-9.

21. Shafrin J, Schwartz TT, Okoro T, Romley JA. Patient Versus Physician Valuation of Durable Survival Gains: Implications for Value Framework Assessments. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2017;20:217-23.
22. National Health Council. *Dialogue/Advancing Meaningful Patient Engagement in Research, Development, and Review of Drugs*. 2015.



PARTNERSHIP TO FIGHT CHRONIC DISEASE

June 10, 2019

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

RE: Public Input for 2020 Value Assessment Framework

Dear Dr. Pearson:

The Partnership to Fight Chronic Disease (PFCD) offers input on ICER's 2020 Value Assessment Framework, with a focus on issues of concern to persons with chronic conditions. PFCD is an internationally-recognized organization of patients, providers, community organizations, business and labor groups, and health policy experts committed to raising awareness of the number one cause of death, disability, and rising health care costs: chronic disease. We appreciate the opportunity to contribute to the evolution and improvement of ICER's practices, models and role in supporting patients and all stakeholders across the healthcare ecosystem to better understand, appropriately assess, and optimize decision-making on value in health and treatment.

Chronic diseases, such as diabetes, COPD, cancer, depression, obesity and heart disease, are the leading causes of death and disability in the United States and account for the vast majority of health care spending. More than one in two American adults lives with at least one chronic condition and nearly one in three live with two or more chronic conditions. Many chronic conditions are preventable and highly manageable.

Yet, chronic diseases are also the primary driver of health care costs—accounting for 90 cents of every dollar we spend on health care in this country. In 2017, this amounted to \$3.15 trillion of the \$3.5 trillion spent on health care.¹ Moving the health care system to one that emphasizes value in the health outcomes and societal benefits achieved is critical to the sustainability of our health care system. That requires a focus on patient-centered and informed strategies for

¹ National Health Expenditures Accounts, CMS, December 2018

understanding health care value and effectiveness holistically, and in support of health care investments and outcomes that have meaning to all Americans.

In seeking public input for its 2020 Value Assessment Framework, PFCD appreciates that ICER identified four core areas of focus that are critical to improving value assessment, including from the perspective of patient experience and what matters most to patients; incorporating patient generated evidence, and, methods to integrate dimension of value not captured by the QALY. We offer the following:

1. Adopt approaches to value assessment that holistically and accurately reflect individual patient experiences and their priorities in health and life.

PFCD recognizes that people living with chronic disease, often with multiple and/or complex conditions, confront challenges in health care nearly every day. For many, barriers seem to arise from a systemic lack of understanding, sensitivity, inclusion, and respect for their unique circumstances in health, health care and life. Current assessment models too often reflect population and large group experience, are generalized, and, as a result, are biased relative to individual patients. Additionally, value calculations that focus on only part of the health care continuum are inconsistent with how people access and manage their health and lead their lives.

People are also more than their condition. A serious flaw in our current health care system is the focus on individual conditions – in our clinical guidelines, in our research institutes, and even in our medical training. But many individuals live with multiple chronic conditions and assessments that only focus on one issue instead of the individual as a whole are destined to fall short. The same holds true of the value assessment frameworks that fail to consider the individuals and populations living with the conditions studied without a full and meaningful assessment of the impact of disease, co-morbidities/complexity, and treatment on the individual as a whole.

People living with chronic conditions have highly individualized and variable experiences with disease, including presentation, symptoms, progression, and the manner in which their bodies respond to certain medicines. Many also have multiple chronic conditions which creates additional complications of treatment. For example, twenty-five (25) percent of all persons with autoimmune diseases have one or more additional autoimmune conditions. For these patients and many others with chronic conditions, Quality-Adjusted Life Years (QALY) and Equal Value of Life Years (evLYG) calculations, which are central to ICER's framework, are grossly inadequate in capturing the patient experience both in living with disease and in the benefits of treatment.

PFCD strongly recommends that ICER include and place a value on the benefits of new treatments from an individual and societal perspective as a substantial core component of all reviews, and that this perspective is visible in the model, deliberations, determinations, summaries, reports, and related communications. A societal perspective should provide a holistic understanding of the persons most closely associated with the treatment under review, with important factors such as functional ability, productivity, caregiver support, and quality of life taken fully into account. That assessment should also include the impact of treatment on people

living with multiple chronic conditions and not be limited to the individual condition studied. Only by more closely reflecting the populations affected and the overall burden of disease and benefit of effective treatment can accurate assessments of value be generated.

The value framework should be improved to reflect timelines that are meaningful to patients. The treatment of many conditions may require large initial costs but generate health, social and productivity benefits over a lifetime. Our view is that value should be measured as the (discounted) health and productivity benefits over a lifetime that result from treatment relative to its costs.

2. Reorient the value assessment framework to assure that patients, including those living with chronic disease, are directly engaged and empowered.

Persons living with one or more chronic diseases and their advocates are uniquely qualified to contribute personal, real-world perspectives concerning health and value. ICER's value framework must put patients at the center of the assessment process to ensure equal, respectful, and meaningful engagement of patients and advocates to yield effective recommendations and results.

PFCD understands that patients living with one or more chronic diseases, disabilities or other conditions are often challenged in balancing their health and treatment regimens, complex financial issues, family responsibilities, school or work, and other commitments. Patient advocacy organizations are often stretched due to limited capacity and resources to engage as fully as they would like to assure that the unique experience and expertise of their constituencies are appropriately taken into account. ICER must be especially attentive to these realities and proactive in bridging any such gaps to assure a truly patient-centered and informed process.

The current ICER framework is undermined by practices that limit patient engagement in voting roles, treat patient input as supplemental or ancillary; insufficiently demonstrate that patient views are actually heard, influential, and are incorporated into final value assessment determinations; or offer arbitrarily short windows for patient and other public comment. Many patient groups report finding ICER's process too complicated to navigate, feel the need to hire economics experts to help them through the process and provide commentary, and find their comments are ultimately ignored.

PFCD encourages ICER to modify its framework to assure that patients with chronic diseases, disabilities, and other conditions and their advocates are fully and equally "at the table" in all aspects of its work. Alignment with models for engaging patients in research at the Patient-Centered Outcome Research Institute (PCORI); including patient representatives in convenings of the National Institute of Allergy and Infectious Disease - Autoimmune Diseases Coordinating Committee; and, in patient-focused drug development at the Food and Drug Administration (FDA) will infuse needed patient expertise, understanding and possibly buy-in to the appropriate role of value assessment in promoting desired health outcomes and investments.

The National Health Council's Patient-Centered Value Model Rubric addresses a range of these issues, recognizing that value models – often viewed as primarily supportive physicians and

payers – can have greater utility by integrating considerations beyond clinical outcomes and cost that are also important to patients – such as the effect of treatment on their ability to achieve life goals.² PFCD concurs with NHC on the critical importance of patient-centeredness in all aspects of value assessment, and recommends that ICER use this tool to evaluate and improve its Framework.

3. Expand the value assessment framework to include and reflect patient-generated evidence.

PFCD recommends the addition of real-world patient data by ICER in its assessment framework and report development to augment and round-out the view provided by randomized clinical trial data to arrive at a more holistic understanding of patients. Increasingly, evidence-based approaches that include patient-reported outcomes, metrics relating to improving outcomes for people living with multiple chronic conditions, and outcomes of primary importance to patients and caregivers are available and essential to generating accurate and balanced assessments that are meaningful to all stakeholders.

The National Pharmaceutical Council and AcademyHealth point out that health researchers have an unprecedented amount of health information available to support studies of real-world data. Electronic health records, clinical data from laboratories, diagnostic testing, claims data, pharmacy dispensing records are among the sources of data that can yield important information about what is working and not working for patients. Yet studies and use of this data in value assessments is often limited by a lack of transparency in research methods.³ PCFD recognizes that while multiple factors influence access and use of such data, we encourage ICER to support steps promoting real-world evidence research methods that are more transparent and appropriate for increasing the utility of such real-world data in its value assessment framework.

With regard to patient-reported outcomes tools, PFCD understands that these frequently portray aggregated data and may fail to reflect changes and/or nuance consistent with an actual patient's real health-related quality of life. However, patient generated evidence – through data collection and analysis, first-person accounts, and full participation as peers in the framework for research, decision-making and reporting – will augment and enhance understanding of health and value. Ultimately, the true understanding of value and any influence on decisions affecting access and affordability of treatment - must be individualized and reflect the best thinking of the patient and his/her physician(s).

For example, patient preferences can offer important insight concerning relative desirability of particular healthcare options, treatment characteristics, and health states.⁴ Yet current methods for establishing patient preference, often cited as foundational to traditional QALYs, are inadequate, generic and unhelpful – especially for persons with chronic conditions. Going

² *National Health Council Shares Guidance for Assessing the Value of New Treatments*; March 28, 2016; www.nationalhealthcouncil.org

³ *Six Ways to Make Real-World Evidence Methods More Transparent*; E.V.I.dently Today Blog; 6/20/19

⁴ Muhlbacher A. *Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions: The European Union Perspective*. Value in Health. 2016

forward, incorporation of real patient preferences as individuals not averages into the process of assessing the value of a set of healthcare options and investments merits attention.

PFCD urges ICER to enhance its assessment framework to more fully empower health care consumers, particularly those with chronic conditions, who are reliant – more than most – on information and access to appropriate, effective and timely care. Patient engagement in research and deliberations, improved transparency, and patient-oriented communications and education will strengthen value assessment and utilization with patients as partners.

4. Improve methods to better integrate non-QALY dimensions of value.

PFCD is very concerned that ICER and others are utilizing models for characterizing value that are too separate and distinct from the multitude of factors that combine to represent health and value for individuals, stakeholders, and systems.

Improved assessment models, if designed correctly and that recognize the importance of personalized care, have potential to improve the management of chronic diseases, slow their spread, and prevent people from developing multiple chronic conditions.

PFCD finds that most currently available quality measures are disease-specific, provider-focused, and process-oriented. There remains a gap of meaningful quality measures that capture what high quality care and favorable outcomes mean for people with multiple chronic conditions. This leads to serious questions about whether quality will be improved for this population, or if patient health could be compromised in the pursuit of cost control. It also casts doubt on judgments of value for treatments or care provided for people with complex health care needs.

The National Quality Forum led development of a framework for quality metrics for multiple chronic conditions in 2012. Yet, we still have few measures that directly relate to commonly co-occurring chronic conditions and lack sufficient infrastructure to collect and utilize patient-reported outcomes as a part of assessments of quality or, ultimately, value. The tools are critically needed to counter cost-cutting measures that sacrifice health and judgments on value that fail to account for quality gains for the patient.

ICER is encouraged to take another look at integrating dimensions of value described as “other potential benefits” and “contextual considerations” in equal standing with or better yet, instead of QALY, to prioritize what is best for each individual patient, particularly those with chronic, often multiple and complex diseases. Incorporation of non-QALY dimensions of value will best support researchers and decision-makers, and adoption of these promising approaches will enhance patient engagement and confidence in results, especially for persons with chronic disease.

* * *

PFCD appreciates the opportunity to provide input on potential changes to ICER's 2020 Value Assessment Framework. PFCD is committed to the health and well-being of people with chronic conditions, their families and all Americans. Ongoing efforts to improve value assessment tools that help patients, physicians, payors, and other stakeholders to make informed decisions about all aspects of health treatments and care are critical.

Respectfully submitted,



Ken Thorpe
Chair, Partnership to Fight Chronic Disease

June 10, 2019

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

Dear Dr. Pearson,

We write representing patients and people with disabilities nationwide living with diverse conditions and diseases, as well as their families, caregivers and providers. We are pleased to provide feedback on ICER's 2020 Value Assessment Framework.

Above all, we urge ICER to put patients and people with disabilities at the center of all of your assessments. While we share your interest in lowering healthcare spending and addressing affordability, we do not believe that generating value assessments in a manner that leads to restricted access and discrimination is a necessary tactic or ethical strategy for achieving these goals. Academics, insurers and policymakers are not capable of determining value to the patient, an unfortunate reality that becomes clear to patients and their providers when coverage decisions based on value frameworks such as those conducted by ICER undermine patient and clinical expertise in decision-making. There are tremendous costs to patients and the health system when we assume all patients are average in a one-size-fits-all healthcare system. Facing restricted access, patients are less adherent to treatments that do not work for them and are more likely to experience adverse events and costly hospitalizations. Ultimately, we support value assessments that decision-makers can use to determine what works for whom and when so that our healthcare system truly drives holistic value in healthcare and minimizes out-of-pocket costs to patients and to the healthcare system.

We encourage ICER to align with innovative leaders in the field. When Congress authorized the Patient-Centered Outcomes Research Institute (PCORI), they created a blueprint for engaging patients and people with disabilities throughout the research process so that it reflected real-world considerations for decision-making. Similarly, the Food and Drug Administration (FDA) has made tremendous progress with patient-focused drug development to identify outcomes that matter to patients and drive innovation to address them. With this in mind, we ask you to consider the following suggestions to update your value framework.

ICER should give patients an equal voice

Last year, Xcenda conducted an analysis to better understand the extent to which ICER meaningfully engages patients and other stakeholders throughout its public comment process. On a positive note, they found that since refining its process for public commenting in 2017, ICER has acknowledged more than 95 percent of comments received from stakeholders. Yet, even when stakeholders proposed solutions that would address their concerns, ICER incorporated only one third (32 percent) of such comments. Comments from patient advocates were least likely to be acknowledged and incorporated (15.9 percent) compared to industry (33.2 percent) and professional/ provider societies (32.6 percent). Patient advocates most frequently commented on adequacy of existing evidence, patient perspective, and

transparency. ICER was more likely to incorporate input on methodology than general feedback on their framework. ICER was least likely to provide a robust response to comments submitted by patient advocates.¹

Patients and caregivers are the only people who can provide essential insight into how living with any one condition impacts their quality of life and what outcomes matter to them in treatment. They are true experts on their condition, yet ICER has chosen to minimize their voices in the review process and generalize patients broadly instead of taking stock of unique considerations for each condition. In fact, ICER does not provide any expert clinicians and patients with the condition being studied with a vote in its final assessments. As ICER develops its updated value framework, stakeholders who have firsthand experience with the specific topic being discussed, either as a patient, caregiver, or clinician, should have an equal voice and vote in all future assessments.

ICER must abandon the use of the QALY and other metrics that treat patients as averages, and, instead, develop novel measures of value to account for patient differences and priorities

The use of quality-adjusted life years (QALYs) and similar summary metrics of cost-effectiveness have long been precluded from use in public health care programs, as they discriminate against patients and people with disabilities by placing a lower value on their lives. For example, Medicare is prohibited by law from using a QALY-based threshold to determine coverage, payment or incentive programs. Health economists from both the United States and other countries have also highlighted that cost-per-QALY should not be the sole method of evaluating new healthcare technologies.^{2, 3}

As you know, utility weights used to derive QALYs rely on survey data. Under population survey models, the non-disabled population may systematically overestimate the burden of life with disability. Illustrating the egregious outcomes that emerge from these types of surveys, research has found a majority of Americans say they would rather have HIV than be blind⁴ and a common QALY measure (EuroQol-5D) rates inflammatory arthritis as “worse than death.”⁵ This issue is particularly visible when ICER’s models include data from studies that use “negative utilities,” such as in the recent study of treatments for secondary progressive multiple sclerosis. It is widely accepted that the logic of having negative utilities for any health state would lead to the contradictory goal of the premature death of a patient resulting in both health gain and being considered a cost-effective intervention. The use of

¹ See

http://www.pipcpatients.org/uploads/1/2/9/0/12902828/pipc_xcenda_icer_stakeholder_mapping_final_report_2018__003_.pdf

² Baltussen R, Niessen L. Priority setting of health interventions: the need for multi-criteria decision analysis. *Cost effectiveness and resource allocation*. 2006 Dec;4(1):14.

³ Thokala P, Devlin N, Marsh K, Baltussen R, Boysen M, Kalo Z, et al. Multiple Criteria Decision Analysis for Health Care Decision Making--An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health*. 2016;19(1):1-13.

⁴ Scott AW, Bressler NM, Ffolkes S, Wittenborn JS, Jorkasky J. Public Attitudes About Eye and Vision Health. *JAMA Ophthalmol*. 2016;134(10):1111–1118. doi:10.1001/jamaophthalmol.2016.2627

⁵ Harrison, M. J., Davies, L. M., Bansback, N. J., McCoy, M. J., Farragher, T. M., Verstappen, S. M., Hassell, A. and Symmons, D. P. Why Do Patients with Inflammatory Arthritis Often Score States “Worse than Death” on the EQ-5D? An Investigation of the EQ-5D Classification System. 2009 Jul; *Value in Health*, 12: 1026-1034. doi:10.1111/j.1524-4733.2009.00565.x

negative utilities can lead to an illogical result whereby a patient's premature death is judged as both a health gain and cost-effective intervention.

A metric based on averages will never adequately reflect patient value, because there is no single perspective on how people see and value "health." With this in mind, it is imperative that ICER looks at the heterogeneity of patient populations, even within the same condition. ICER's focus on developing tools for payers misses the bigger picture – that high-quality individualized health care increases treatment adherence and allows patients to care for their families and meaningfully participate in communities and the workforce, a cost-effective strategy that recognizes the value of all lives as worthy of treatment.

The newly developed evLYG does not fix the problem. While the evLYG partially mitigates the life-extension problem – if insurers use it – it still offers payers a means of refusing access to an effective and beneficial drug by using a summary metric that fails to account for outcomes that matter to patients. The evLYG does not address the challenges described above related to undervaluing quality of life improvements or ignoring clinical knowledge. This kind of QALY-based system remains less effective than condition-specific means of assessment.

In response to stakeholder opposition to the use of the QALY, ICER's response has been that the QALY is the "gold standard."⁶ Discrimination is not the gold standard. We join the chorus of stakeholders that have implored ICER to move beyond QALYs and urge ICER to instead follow the lead of other organizations that are advancing truly innovative value assessment models that are open-source, transparent, and able to generate disease-specific information using methods such as multi-criteria decision analysis.

ICER should have more stringent standards for minimum data requirements to conduct a review and continually revise each review based on new data

Pressure to immediately deliver payers and policymakers with assessments upon FDA approval has led to ICER undertaking its reviews at a stage when adequate data is unavailable. Its subsequent cost-effectiveness models rely on assumptions, oversimplified models, and incomplete data more than would be acceptable under a traditional peer-reviewed process. By prioritizing speed over quality, ICER provides payers and policymakers with flawed information based on limited evidence, which will lead to decisions that are similarly flawed. For example, ICER's methods for assessing treatments for spinal muscular atrophy put patients into three buckets: (1) sitting and walking, (2) need for permanent ventilation, and (3) death. Yet, SMA is a complex illness, and this overly simplistic categorization does not capture the experiences and health gains of all patients nor the value for patients and families from incremental improvements in quality of life.

In order to address this issue, ICER should incorporate in its framework a minimum data requirement for when a review may be conducted and refrain from publishing a value-based price until it is able to determine the "impact on net health benefit" with "high certainty." While doing so will not resolve the implications for discrimination and lack of transparency, it would be positive step to ensuring adequate data is utilized. Additionally, ICER should clarify the limits of its studies at the stage of their

⁶ See <https://icer-review.org/announcements/icer-describes-qaly/>

development and the inability of ICER's model to consider certain patient-centered endpoints that may not yet be reflected in research literature.

ICER should also make a commitment to update its estimated cost-effectiveness results each time new data becomes available on key inputs of cost and effectiveness. In particular, this should include the incorporation of real-world prices, real-world data on outcomes, and quality of life data specific to populations who have been treated with the drug under investigation. These real-world data sources have become ever more important, as the FDA sees real-world data as a key component of evaluating the potential value of new indications in approved therapies.⁷

Other value frameworks have also acknowledged the importance of real-world data that provide robust patient-centered information beyond the limits of randomized clinical trials. For example, the Patient Perspective Value Framework (PPVF), which has been developed by a coalition of stakeholders over the past three years now, has resulted in a framework to assess the benefits and costs of different healthcare options in the context of patients' personal goals and preferences.⁸ The PPVF recently released long-term recommendations provide strong guidance for aggregation and utilization of rigorous real-world data, providing ICER, payers, policymakers, and others with guidance on how to actually achieve real-world data and incorporate it into real-world decision-making.⁹ We are hopeful that ICER and its payer customers will be part of the solution to relieve patients and physicians from restricted access to valuable healthcare innovations that emerge from use of value assessments such as those currently developed by ICER that are built on inadequate and outdated data. With a strong commitment to updating its evaluations as real-world data emerges, such calculations would not need to rely as much on assumptions and RCTs that fail to reflect subpopulations.

ICER's models should be open-source, transparent, and available to all patients and researchers

ICER's assessments are a black box, leaving patients and people with disabilities in the dark on assumptions and important limitations that impact their results. An open-source version of the model where stakeholders can evaluate the different input choices, assumptions, and model structures would assure they are fair and unbiased. It would also allow stakeholders to submit more instructive and informed feedback. We are encouraged that organizations such as the Innovation and Value Initiative (IVI) are advancing open-source models and encourage ICER to follow their lead.¹⁰ Patient groups have consistently called on ICER to be more transparent about the limitations, model design, and evidence used for ICER's assessments. As ICER has heard before, the validity and reliability of ICER reports can be difficult to determine because the inputs used are often opaque.¹¹

In tandem with this, ICER needs to allow more time for stakeholders to submit public comments. ICER takes three months to develop a draft report and another two to produce a final report, yet public

⁷ https://cancerletter.com/articles/20190419_2/

⁸ See http://go.avalere.com/acton/attachment/12909/f-047c/1/-/-/-/20150510_PPVF%20Infographic_Print%20Friendly.pdf

⁹ Insert footnote when available

¹⁰ See <https://www.thevalueinitiative.org>

¹¹ See comments by Alliance for Aging Research at http://icer-review.org/wp-content/uploads/2016/10/ICER_Comments_on_VAF_100316.pdf

comments are generally restricted to three weeks. This short timeline does not allow stakeholders adequate time to properly evaluate the chosen inputs and understand how they interact within model structures.

It is important for ICER to recognize that patient groups, particularly for rare diseases, have limited bandwidth within their small organizations. Meaningful engagement in an ICER report process requires a significant investment by patient groups for whom it is vitally important that ICER's work not undervalue treatments and thereby result in restricted access. Yet, given the lack of transparency and limited description of the model components in the reports, it would take months and significant investment for a stakeholder to build a model based on the report and thoroughly evaluate it. While patient groups do the best they can, this inevitably means that meaningful input and critique of the models is seriously limited, and patient groups and the experience of their members become marginalized as a result. This has been noted to ICER in past comment letters. For example, the MS Coalition urged ICER "to consider ways to make the comment periods friendlier to patients by offering companion draft reports at an appropriate health literacy level for the general MS population" in their comments on the Secondary Progressive Multiple Sclerosis (SPMS) study.¹² If ICER wishes to learn from the public comments, then it is beholden to make that process accessible. ICER's current process for stakeholder feedback demonstrates the limited value they place on receiving thoughtful criticism or commentary on its methods.

ICER must incorporate a range of patient-relevant outcomes and reflect the range of potential levels of effectiveness new treatments have across a heterogeneous patient population

Rather than prioritizing outcomes that matter to patients and people with disabilities in its studies, ICER values a treatment from the health system and insurer perspectives. This misaligns ICER against the best practices within its own field and can lead to situations where it is judged more "valuable" to **not** provide additional care or certain treatments for some patients because doing so would not be "cost-effective."

While patient-reported outcomes are an essential step in the right direction for patient-centered research, even patient-reported outcome (PRO) tools are often insensitive to changes in actual patients' real health-related quality of life (HRQoL).¹³ Some studies have shown that patients often highlight very different areas of concern than those that dominate weights in HRQoL studies.^{14 15} This information alone should make ICER question using the QALY while ignoring outcomes that matter to patients. The National Alliance on Mental Illness (NAMI) highlights this in its November comment letter to ICER on its study on Treatment Resistant Depression (TRD), noting that patients with TRD place high priority on

¹² See https://icer-review.org/wp-content/uploads/2018/10/ICER_MS_Draft_Scope_Comments_112918.pdf

¹³ Schafer K, De Santi S, Schneider L. Errors in ADAS-cog administration and scoring may undermine clinical trials results. *Current Alzheimer Research*. 2011 Jun 1;8(4):373-6.

¹⁴ Jones PW, Rennard S, Tabberer M, Riley JH, Vahdati-Bolouri M, Barnes NC. Interpreting patient-reported outcomes from clinical trials in COPD: a discussion. *International journal of chronic obstructive pulmonary disease*. 2016;11:3069.

¹⁵ Urquhart-Secord R, Craig JC, Hemmelgarn B, Tam-Tham H, Manns B, Howell M, Polkinghorne KR, Kerr PG, Harris DC, Thompson S, Schick-Makaroff K. Patient and caregiver priorities for outcomes in hemodialysis: an international nominal group technique study. *American Journal of Kidney Diseases*. 2016 Sep 1;68(3):444-54.

treatments that offer fast, effective relief, and the ICER model fails to capture this by using a model that does not account for esketamine's immediate impact.¹⁶ The Asthma and Allergy Foundation similarly questioned whether the assumptions ICER made in its economic analyses meaningfully reflect the actual experience of asthma patients using biologics or any subpopulations of this group.¹⁷

In addition, ICER's practice of reporting outcomes as population-wide estimates runs counter to the direction in which medicine and the health care system is moving. The emergence of personalized medicine presents a paradigm shift to a world where innovations in medicine no longer treat a disease, they treat that disease in a specific person or population. As clinical decision making evolves in that direction, the methodology for interpreting and reporting evidence on value of innovations should evolve with it. It is imperative that ICER catch up to contemporary medical innovation and reflect evidence on heterogeneity, as it is well established that generating and reporting differential value assessment across subgroups will lead to substantial health gains.^{18, 19} Simply reporting estimates for overall populations – despite clinical evidence showing differential effectiveness across sub-populations – leads to a disconnect between how evidence is interpreted by payers versus clinicians and patients. This disconnect can ultimately lead to inefficient decision-making and loss of health gain.

Conclusion

Thank you for your consideration of our suggestions on ways in which ICER can make its value assessments fairer and more equitable to patients. Please feel free to reach out to Sara van Geertruyden (sara@pipcpatients.org) in response to our recommendations above.

Sincerely,

Aimed Alliance
Alliance for Aging Research
American Academy of Physical Medicine &
Rehabilitation
American Association of People with Disabilities
American Association on Health and Disability
Arthritis Foundation
Asthma and Allergy Foundation of America
Autistic Self Advocacy Network
Bridge the Gap - SYNGAP Education and Research
Foundation
Cancer Support Community
CancerCare
Coelho Center for Disability Law, Policy and Innovation

¹⁶ See https://icer-review.org/wp-content/uploads/2018/10/ICER_TRD_Draft_Scope_Comments_112918.pdf

¹⁷ See <https://www.jmcp.org/doi/full/10.18553/jmcp.2019.25.5.514>

¹⁸ Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered healthcare. *Journal of Health Economics* 2011; 30(3): 549-559.

¹⁹ Espinoza MA, Manca A, Claxton K, Sculpher MJ. The value of heterogeneity for cost-effectiveness subgroup analysis: conceptual framework and application. *Medical Decision Making*. 2014 Nov;34(8):951-64.

Diabetes Patient Advocacy Coalition
Epilepsy Association of North Carolina
Epilepsy Foundation
Global Liver Institute
GO2 Foundation for Lung Cancer
Haystack Project
Headache and Migraine Policy Forum
Heart Valve Voice
Lakeshore Foundation
Lupus and Allied Diseases Association, Inc.
LUNGevery Foundation
National Alliance on Mental Illness
National Council on Independent Living
National Diabetes Volunteer Leadership Council
National Infusion Center Association
National Minority Quality Forum
Not Dead Yet
NTM Info & Research
Partnership to Improve Patient Care
Philip Posner
Rosie Bartel
Southern Maine Chronic Pain Support Group
The Arc of the United States
The Association of University Centers on Disabilities
Whistleblowers of America



June 10, 2019

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

by electronic delivery

Re: Comments on the 2020 Value Assessment Framework

Dear Dr. Pearson:

The Personalized Medicine Coalition (PMC) appreciates the opportunity to submit comments regarding the forthcoming draft revisions to the Institute for Clinical and Economic Review (ICER)'s value assessment framework, to be published in August of 2019.

Comprised of over 200 member institutions from every sector of the health care ecosystem, PMC, an educational and advocacy organization representing patients, providers, payers, innovators, and scientists from around the world, promotes the understanding and adoption of personalized medicine concepts, services, and products to benefit patients and the health system.

Personalized medicine is an emerging field that uses diagnostic tools to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will work best for each patient. By combining this information with an individual's medical records, circumstances, and values, personalized medicine allows doctors and patients to develop targeted prevention and treatment plans.

PMC's primary interest is in the extent to which proposed updates to ICER's value assessment framework, herein called the framework, reflect a consideration of the value of personalized medicine products, services, and concepts. Considerations related to personalized medicine can significantly impact the assessment of comparative clinical effectiveness and comparative value. Treatments that are targeted for use based on a patient's molecular characteristics and individual circumstances improve outcomes by allowing physicians to provide the most effective and safest treatment to each patient as early as possible. Doing so may in turn bring down costs by helping to avoid ineffective or harmful treatment options and reducing the downstream expenses associated with rapid disease progression and/or adverse events.

BOARD OF DIRECTORS

President

Edward Abrahams, Ph.D.

Chair

Stephen L. Eck, M.D., Ph.D.
Immatics Biotechnologies

Vice Chair

Jay G. Wohlgemuth, M.D.
Quest Diagnostics

Treasurer

Peter Maag, Ph.D.
CareDx

Secretary

Kimberly J. Popovits
Genomic Health

Bonnie J. Addario
GO2 Foundation for Lung Cancer

Antoni Andreu, M.D., Ph.D.
EATRIS

Steven D. Averbuch, M.D.
Bristol-Myers Squibb Company (ret.)

Randy Burkholder
PhRMA

William S. Dalton, Ph.D., M.D.
M2Gen

Lori Frank, Ph.D.
Alzheimer's Foundation of America

Brad Gray
NanoString Technologies

Kris Joshi, Ph.D.
Change Healthcare

Anne-Marie Martin
Novartis

Susan McClure
Genome Creative, LLC

Howard McLeod, Pharm.D.
Moffitt Cancer Center

J. Brian Munroe
Bausch Health Companies

Lincoln Nadauld, M.D., Ph.D.
Intermountain Healthcare

Michael Pellini, M.D., M.B.A.
Section 32

Hakan Sakul, Ph.D.
Pfizer, Inc.

Michael S. Sherman, M.D., M.B.A.
Harvard Pilgrim Health Care

Mark P. Stevenson
ThermoFisher

Sean Tunis, M.D.
Center for Medical Technology Policy

Werner Verbiest
Johnson & Johnson

To this end, PMC recommends that ICER recognize five principles as it continues to consider concepts related to personalized medicine within the framework:

1. Considerations related to personalized medicine, such as heterogeneity of treatment effect, treatment efficiency (i.e., potential cost savings by avoiding less effective treatment or adverse side effects), and individual values and circumstances can significantly impact comparative clinical effectiveness and value assessment.
2. Diagnostic testing must be considered an integral part of the assessment of the value of treatment options where heterogeneity of treatment effect can be assessed, or efficacy and/or safety information can be obtained.
3. Methods for assessing value must consider real-world evidence (RWE) that can provide insight on emerging or evolving value elements over time.
4. Valuation approaches should be transparent and consistent and include a broad array of benefits that are important to patients and society.
5. All stakeholders must be engaged, and multiple perspectives must be integrated throughout the value assessment process in order to encompass all value elements that need to be considered in the assessment of various treatments to the health care system.

Statement of Neutrality

Many of PMC's members will present their own responses to ICER and will actively advocate for those positions. PMC's comments are designed to provide feedback so that the general concept of personalized medicine can advance, and are not intended to impact adversely the ability of individual PMC members, alone or in combination, to pursue separate comments with respect to the proposed updates to the value assessment framework or related issues.

General Comments Regarding the Framework

We offer these comments about how the scope of the framework may affect the field of personalized medicine.

The Population Perspective, Heterogeneity, and Intended Uses

The framework is intended to inform medical policies through a population-level perspective. ICER should not conflate, however, the impact of a therapy on patient health outcomes with the potential budget impact to any individual stakeholder or stakeholder group. We acknowledge ICER's statement that stakeholders focused on population-level decision-making, including payers and policymakers, are the intended audience of its value assessments. This does not discount or diminish, however, other key perspectives of value.

ICER should consider, for example, how assessing the value of different therapies to individual patients could facilitate improvements and efficiencies at the population level by ensuring that only those

patients

who are most likely to benefit from new therapies actually receive them. The final decision of which therapy, or combination of therapies, is most appropriate for a patient must (1) be left to the patient working with his or her provider; (2) involve consideration of the patient's clinical circumstances; and (3) involve consideration of a therapy's long-term impact on a patient. Utilizing personalized medicine strategies, providers are able to identify individuals within larger populations that are more or less likely to respond to certain therapies. Therefore, inclusion of these considerations should, on balance, lead to population-level efficacy, safety, and efficiency.

Value Factors

We recommend that the framework examine a broad range of factors specific to each evidence review within the appropriate context to inform and support determination of high-value care. This may include short-term

affordability and long-term value, but these factors alone are insufficient. Furthermore, the valuation of sustainable access to high-value care falls short of a complete societal perspective of value (Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahm M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016 Sep 13;316(10):1093-103). The societal perspective may often incorporate factors such as productivity and caregiver burden. A societal perspective will ensure that all patient- and societal-focused benefits are included, not just those that will be accrued by the payer. Elements such as systemic efficiency (i.e., getting the right treatment to a patient as early as possible), the contribution of innovation to the further advancement of medicine, and the contribution of an innovation to an evolving care paradigm should be taken into consideration.

Length of Time for Review

While we appreciate that the timelines for responding to proposed process updates have been increased, they are often still insufficient for the purpose of soliciting feedback from multi-stakeholder coalitions like PMC. PMC and its members can support ICER by providing in-depth, technical insights on the subject matter of ICER's evaluations. As a coalition, any insights we offer must represent the interests of a range of disciplines and balance the perspectives and needs of our many members. Meanwhile, the field of personalized medicine is moving at an incredibly rapid pace. In this context, it is impractical for many stakeholders, particularly coalitions like PMC, to fully react to and respond to ICER's complex and lengthy reports in a short period of time. The length of open comment periods should reflect the importance, length, and complexity of the items to which the community is responding.

Furthermore, ICER does not allocate an adequate amount of time to its own review and reaction to stakeholder comments. PMC reiterates its recommendation that all comments submitted to ICER and their disposition should be publicly available. ICER should give its rationale for issues that it has chosen not to incorporate or address. Longer timelines for ICER's review and consideration of stakeholder input, and unlimited length requirements related to stakeholder feedback, will allow for greater community acceptance of ICER's assessments.

Comments Regarding Specific Areas for which ICER is Requesting Input

We appreciate ICER's call for comments on how to improve the framework and efforts through prior framework revisions that have provided greater alignment with personalized medicine practices and principles; however, further revision and refinement of the framework in this area is warranted to ensure the applicability and usefulness over the period during which the updated methodology will be implemented. Key recommendations related to ICER's specific requests for input are highlighted below.

Cost-effectiveness thresholds

ICER has implemented a range of incremental cost-effectiveness thresholds, which are determined based on the average weighting of pre-specified elements or other benefits and contextual considerations voted on and ranked by an independent committee. It should be recognized that no single metric threshold can or should be universally applicable, as thresholds are likely to vary by decision-maker, population, and disease. Furthermore, ICER's current approach of setting a uniform budget impact threshold based on a fixed portion of drug expenditures creates an artificial affordability threshold that could have negative, unintended consequences such as shifting spending toward lower cost care that is less efficient, thereby moving away from personalized medicine and reducing the value of our health care dollar.

The approach ICER takes to evaluate the magnitude and certainty of net health benefit

Inclusion of Evidence and Process Updates

The next iteration of the framework will impact ICER evidence reports for all assessments initiated in 2020 and beyond. Personalized medicine considerations will affect many, if not all, of ICER's value assessments going forward, as evidenced by the fact that over the last four years (2015 – 2018), personalized medicines have accounted for more than 25 percent of all new drug approvals, and the number of newly approved personalized medicines is expected to continue to grow (Personalized Medicine Coalition, *Personalized Medicine at FDA: A Progress and Outlook Report*: http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_at_FDA_A_Progress_and_Outlook_Report.pdf).

Evidence review of clinical outcomes within the framework is mostly limited to data accumulated for a product up to its market launch. This does not take into account emerging value factors and evidence accumulated after product launch. New and emerging technologies are disadvantaged in assessments where the framework compares the value of established products vs. that of emerging products (e.g., pre-launch, new to market) since only early indicators of efficacy, safety, and value are acknowledged.

The personalized medicine field is evolving too rapidly to accurately maintain a current assessment of treatment value with a two-year period between assessment reviews and updates. For example, shortly after ICER published its report on the value of non-small cell lung cancer treatments, technology advancements related to the use of biomarkers to help guide treatment decisions altered the value proposition for some treatments. For a value assessment framework to remain useful over time, evidence reports

need to be updated more routinely. ICER should provide criteria for when evidence reviews will be updated based on new evidence, particularly as it relates to diagnostic stratification or other contextual factors. The framework should consistently employ methods to assess value at interim time points over a longer term using practice-based evidence wherever possible.

Randomized Clinical Trials and Real-World Evidence

We appreciate the steps ICER has taken to open the framework to the inclusion of a broader range of data sources for assessments, extending beyond randomized clinical trials (RCTs) to include, for example, RWE and grey literature. RCTs have great value in determining clinical safety and efficacy of therapies, but value can differ when viewed through the lens of actual practice in the real-world situation. It is unclear how these data will be incorporated into ICER evaluations, models, and value metrics, but it is important that RWE carry an appropriate amount of weight in evaluations and that this is defined *a priori* in the framework. Furthermore, conducting RCTs for some personalized medicines is not feasible because it would be impossible to develop a large enough cohort of patients with a rare genetic variant necessary to demonstrate clinical significance. In these cases, RWE is instrumental to the personalized medicine value assessment. The evidence landscape is evolving away from the traditional RCT. With the growing focus on personalized medicine, smaller patient populations make them harder and more expensive to conduct. Finally, RWE can also provide information on how patients who may often be excluded from RCTs due to co-morbidities or other criteria may benefit from a therapeutic in routine clinical practice.

Report Development and Stakeholder Engagement

PMC commends ICER on efforts to further engage stakeholders on policy development, both in recent value assessment reports and in the proposed revisions to the framework. Consideration of perspectives of all personalized medicine community stakeholders, especially patients and caregivers, is critical to getting the right treatment to each patient as early in their care as possible. However, we respectfully note room for greater engagement that can more completely integrate patients and other critical stakeholders into the value assessment process. In order to truly encompass and reflect clinical real-world experience and value to patients, these stakeholders' perspectives must be integrated throughout the process.

To encourage continued high-quality input, PMC recommends that ICER make the process for communication with patients and caregivers clear. We are pleased that ICER increasingly provides opportunities for patients to engage throughout a value assessment and to submit data. To complement ICER's Patient Open Input Questionnaire, ICER should clearly emphasize and describe the patient-provided information that would be valuable for patient groups to collect. The earlier that patient groups are aware of a call for feedback and what types of input/data collection will be useful, the better they can accommodate these requests. Data quality may also be improved.

The use of QALY and the evLYG

We appreciate that ICER has made efforts to broaden its cost-effectiveness analyses, focused on cost per life year

gained and cost per quality-adjusted life year (QALY), to permit consideration of alternate, or additional, cost-effectiveness and cost-utility measures, which may capture important disease-specific outcomes such as cost per consequence, when relevant.

While the QALY's ability to provide a single measure of the "value" of a treatment makes it a commonly used metric for quantifying health benefits, patients do not receive treatments in isolation. Personalized medicine is a complex, multifaceted process with patients receiving care along a continuum — from diagnostic testing, clinician and genetic counselor consultation, disease management and monitoring, to medication therapy and hospitalization when necessary.

A single measure cannot adequately capture true patient-centered value and the broad heterogeneity of clinically relevant characteristics and preferences across patients and diseases. PMC therefore recommends disaggregating the single-value metric and considering a more comprehensive set of value elements that is inclusive and reflects personalized medicine services and concepts as well as individual patient circumstances.

Methods by which to integrate potential benefits, contextual considerations, and other factors

Contextual Considerations

ICER maintains that "Evaluations of long-term cost-effectiveness are made challenging because of the potential for evolution of devices/diagnostics and the attendant changes in cost, effectiveness, and the types of patients that will be treated." ICER answers this challenge by incorporating specific unique approaches to evidence evaluation and use of diagnostic interventions as contextual considerations. While we appreciate that ICER recognizes the potential for these elements to impact value, and the potential for the evolution of treatment value due to devices/diagnostics, the consideration of "contextual considerations" falls short of adequately capturing the value factors that may be realized due to diagnostic tests. For example, the framework does not explicitly include value factors related to predictive testing to (1) avoid ineffective treatment initially; (2) make an informed change in treatment when patients fail to respond; or (3) determine clinical trial eligibility — all of which are critical elements of the evolving treatment landscape and help build evidence of value of novel drugs.

Appropriate Consideration of Diagnostic Tests

The framework does not have a formal, consistent approach for the consideration of diagnostics intended to help guide treatment decisions where appropriate. The framework considers "evaluation of diagnostic tests and delivery system interventions by taking into account their unique nature or circumstances," but the framework does not specifically call on assessments to consider validation, utility, and economic impact of diagnostic tests. Guidelines for a consistent approach should consider (1) when diagnostics should/should not be included in assessment processes, (2) how (methodologically) diagnostics are included in the evidence review and economic evaluations, and (3) implications and standards for analyzing and reporting on patient subgroups.

Diagnostic testing in personalized medicine is a key step on the path to getting the right medicine to a patient as

early as possible. It is imperative that the framework considers testing an integral part of clinical decision-making by which efficacy and safety information of treatments can be obtained. The detection or measurement of biomarkers plays an important role in determining value across numerous clinical scenarios, many of which are subject to rapidly advancing scientific knowledge. The context of biomarkers within clinical scenarios must therefore be figured into the framework's methodology. Failure to explicitly address this important component of value at this time will undermine the usefulness and applicability of the framework going forward.

Valuation Approaches

The relative contribution to the overall long-term value of these contextual considerations, and other benefits and disadvantages, is subjective. Relying on contextual considerations thereby risks applying false weight and a false sense of precision and accuracy to these subjective value elements. The subjective relative ranking scale proposed by ICER may unfairly undervalue innovative personalized medicines, as it may be particularly problematic for newer treatments and therapies where evidence of societal and contextual benefits may be lacking at the time of assessment. ICER's current approach leaves the consideration of these factors up to the discretion of the voting panel, which may not have the expertise or appropriate context to meaningfully evaluate them. Because it is heavily dependent upon the perspectives and decisions of a small group, this valuation approach is not transparent or consistent. Furthermore, the approach may be insufficient to incorporate the impact of important patient-centered factors.

PMC strongly advocates that ICER devise a method to formally account for these elements with a fully transparent valuation approach that incorporates viewpoints from all stakeholders to assure that specific value elements are appropriately considered in evaluations and that they account for emerging evidence.

Conclusions/Recommendations

Personalized medicine has a profound impact on the comparative value of treatments, and now is the time for ICER to formally address, take into consideration, and clearly delineate the methods for integrating personalized medicine products, services, and concepts into the framework. We look forward to working with you to improve ICER's process so that the principles of personalized medicine (getting the right treatment to a patient as early in their care as possible) are incorporated into its work.

With these five principles in mind, the framework can better reflect and serve the needs of the health care community:

1. Considerations related to personalized medicine, such as heterogeneity of treatment effect, treatment efficiency (i.e., potential cost savings by avoiding less effective treatment or adverse side effects), and individual values and circumstances can significantly impact comparative clinical effectiveness and value assessment.
2. Diagnostic testing must be considered an integral part of the assessment of the value of treatment options where heterogeneity of treatment effect can be assessed or efficacy and/or safety information can be obtained.

3. Methods for assessing value must consider RWE that can provide insight on emerging or evolving value elements over time.
4. Valuation approaches should be transparent and consistent and include a broad array of benefits that are important to patients and society.
5. All stakeholders must be engaged, and multiple perspectives must be integrated throughout the value assessment process in order to encompass all value elements that need to be considered in the assessment of various treatments to the health care system.

PMC appreciates the opportunity to provide these comments. PMC and ICER are united by a shared goal of providing patients and health care providers with safe and effective technologies that will best serve the needs of patients and the health care system. If you have any questions about the content of this letter, please contact me at dpritchard@personalizedmedicinecoalition.org or (202) 787-5912. We look forward to further opportunities to provide feedback.

Sincerely yours,



Daryl Pritchard
Senior Vice President, Science Policy
Personalized Medicine Coalition



Pfizer Inc
235 East 42nd Street
New York, NY 10017

June 10, 2019

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109
Submitted via email: publiccomments@icer-review.org

RE: Public Input for 2020 Value Assessment Framework

Dear Dr. Pearson:

On behalf of Pfizer Inc., thank you for the opportunity to comment on the 2020 ICER Framework. Pfizer is committed to discovering medicines and vaccines that enhance the health of patients, their families, and society. At the same time Pfizer is committed to identifying solutions for creating a more effective, efficient, and equitable health care system in the US.

We appreciate ICER's efforts to evolve its value assessments and its call for comments on the 2020 Value Assessment Framework from a variety of stakeholders. Accurately assessing and establishing the value of medicines is a complex undertaking, and thus deserves careful attention and continuous effort. This is a very important opportunity to appropriately update the value framework so that 1) value is treated as a heterogenous assessment; 2) patients voice is appropriately included; 3) the complexity of US health care is more robustly captured; 4) and the changing nature of the transformative medicines being developed and brought to patients by the biopharma industry today are appropriately assessed.

We acknowledge ICER has already made some improvements to its value framework (e.g. starting to include patients' perspective, asking for various stakeholder inputs, and sharing health economic models). However, we believe that the current framework is still not appropriate to assess the value of medicines in the U.S. health care system.

In our comments we will address the following issues:

1. *Limitations of Quality-Adjusted Life Years (QALYs) and importance of including additional benefits and patients provided information (PPI)*
2. *Value-based price benchmark and use of arbitrary cost-effectiveness thresholds*

3. *Disease economic modeling transparency and validity by engaging with manufacturers, key clinical experts, and patients*
4. *Inclusion of Real-World Evidence (RWE) to fully understand the value of medicines to patients and society*
5. *Rationale for removing budget impact assessment from the value assessment*

1. Limitations of the QALY approach and importance of including information provided by patients

Since patients are the final decision makers of whether to fill a prescription and adhere to its dosing schedule or not, patient provided information (PPI) are critical inputs for the full assessment of value of any medicine. PPI provides insights into what is relevant for patients and their risk-benefit assessment which may differ from that of regulators and physicians. The FDA has a variety of initiatives in place for systematically capturing patients' experiences, perspectives, needs, and priorities into drug development and evaluation¹. Therefore, we recommend including PPI in the economic value assessment in addition to gathering patients' opinion during the Comparative Effectiveness Public Advisory Council (CEPAC) open meeting.

Highlighting non-clinical benefits and contextual considerations that may be relevant in assessing the value of a medical intervention is often insufficient to capture the totality of evidence for patients, families and the parts of society impacted by the disease under assessment. This nuance is generally lost in the summaries and press releases which is why it is important to include this in the model directly. The value-based price (VBP) derived from the base case model in these summaries is unable to paint a clear picture of how these additional benefits are perceived and weighted by patients, and of how improvements to their lives may be directly attributable to the therapies reviewed.

In addition, QALYs are not a proxy for patients' perspective and they should not be used as such. The shortcomings of QALYs are well recognized among health economists, policy makers, insurers, and patients^{2,3,4,5}.

The Second Panel on Cost Effectiveness (Neumann et al. 2017)⁶ emphasized the need to add more elements of value to QALYs to address these shortcomings and better assess value. The societal

¹ FDA. *Patient-Focused Drug Development*. <https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development>

² Neumann and Cohen (2018). "QALYs in 2018-Advantages and Concerns". JAMA 319(24):2473-2474.

³ Perfetto (2018). ISPOR's Initiative on US Value Assessment Frameworks: A Missed Opportunity for ISPOR and Patients. *Value in Health* 21, 169-170.

⁴ Solow and Pezalla (2018). ISPOR's Initiative on US Value Assessment Frameworks: The Use of Cost-Effectiveness Research in Decision Making among US Insurers. *Value in Health* 21, 166-168.

⁵ Pettitt et al. (2016). The Limitations of QALY: A Literature Review. *J Stem Cell Res Ther*. 6(4) 1-7.

⁶ Neumann et al. (2017) "Cost-effectiveness in Health and Medicine. Second Edition". Oxford University Press.

perspective, which brings a broader point of view, needs to be the reference case. The payer's perspective can be used as a parallel reference case or a scenario analysis. The societal perspective should include elements such as informal health care sector costs and relevant non-health care sector costs (Pfizer recognizes that the inclusion of social services, consumption, legal/criminal, justice, education, housing, and environment may be relevant only for specific diseases and conditions).

Moreover, since QALYs by default underestimate the value of medicines and treatments for very severe conditions - the more severe the illness, the greater the error (Lakdawalla, et al.)⁷-. If ICER decides to use QALYs, the analysis should also include insurance value and value of hope especially for very severe diseases. The insurance value and value of hope involve inclusion of patient preferences and assessment of risk aversion. Lakdawalla and team have developed the "Quality- and Risk-Adjusted Life-Year" (QRALY) to adjust QALYs and include value of hope and insurance value. The QRALY can be used just like a standard QALY in incremental cost effectiveness ratios.

We acknowledge that ICER has tried to identify an alternative to QALYs, given the shortcomings, by including a supplementary equal-value life year gained (evLYG) analysis. However, the evLYG has a number of shortcomings, and does not solve the deficiencies of QALYs. For example, a medicine that does not prolong life (for example a cure for blindness) would not have any value when assessed using evLYG. Innovative medicines' value is not just about prolonging life, it is about addressing patients' unmet need and improving population health and wellbeing.

ICER should not be content to use simply the best option that exists today to measure value but should lead initiatives to build a better solution through a separate assessment. Quantitative benefit-risk metrics that include patient preference weighting should be considered. It is critical that ICER vigorously works to improve the way they measure the value of medicines through collaboration with other stakeholders if they intend to comment on value-based prices and justifiable price increases. This call for comments on the 2020 value framework is a good start in that direction but we can no longer rely on the justification that there is no better way to measure value to continue using outdated and biased tools.

Pfizer's recommendation is that societal elements of value are included in the reference case for any ICER cost-effectiveness calculation and not just for rare diseases as recommended also by the second panel on CE. Moreover, we recommend that QRALY are used as a scenario analysis to test differences and limitation of the QALY approach by including the insurance value and the value of hope into the

⁷ Lakdawalla et al. (2016) "The Insurance Value of Medical Innovation." NBER Working Paper Series, March 2015

analysis. Moreover, new tools should be evaluated to address the shortcomings of current tools as the evLYG supplementary analysis is not the solution to QALYs problems.

2. Value-based price (VBP) benchmark and use of arbitrary affordability thresholds

The presentation of one single VBP benchmark for different thresholds does not capture the heterogeneity and complexity of the US health care system, perception of value by different stakeholders, and uncertainty in the analysis. Value assessment includes a variety of elements as emphasized by the “value flower” developed by Lakdawalla, Garrison et al.⁸

Value assessment varies depending on:

- disease severity and age of patient with the disease
- presence of alternatives
- patient/clinician assessment of risk-benefits for each medication
- family and societal implications
- value of scientific innovation
- priorities and affordability challenges of the different stakeholders

Finally, Pfizer would like to mention that the current cost-per-QALYs threshold is not based on any scientific rationale⁹. Thresholds should vary by disease severity and by willingness to pay or opportunity costs of different stakeholders. A willingness to pay for a chronic condition affecting individuals aged 80 years or older may be very different than the willingness to pay for a condition affecting a child or a young mother.

Therefore, Pfizer believes thresholds should not be used as they are arbitrary. If ICER decides to still use thresholds, Pfizer recommends that uncertainty about thresholds for various diseases and scenarios be addressed in the short term through a workshop with health economists, payers, and patients to identify TA-specific cost-per-QALY thresholds, and in the long term by developing and testing alternative value assessment methodologies. Moreover, Pfizer recommends that a range of VBP is presented for each threshold to fully represent the potential value of a medication for different stakeholders. The final decision of what is the most relevant VBP should be left to each stakeholder depending on the relative importance they allocate to the different elements of value and their specific affordability challenges.

⁸ Lakdawalla et al (2018). "Defining Elements of Value in Health Care - A Health Economics Approach: An ISPOR Special Task Force Report [3]." *Value in Health*, vol. 21, no. 2, pp. 131-139.

⁹ Grosse (2008). Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY threshold. [Expert Rev Pharmacoecon Outcomes Res.](#) 2008 Apr;8(2):165-78.

3. Enhance the transparency, replicability, and validity of disease economic models by engaging with manufacturers, key clinical experts, and patients

Pfizer applauds ICER for running a pilot to assess the feasibility of sharing disease modeling with manufacturers. Pfizer recommends that moving forward this become the norm.

A cost-effectiveness model is a representation of the clinical and patient journey through the health care system and unfortunately no model can completely represent the complexity of reality, but any effort should be made to represent this journey as closely as possible. As stated by Sir Box “all models are wrong, but some are helpful”¹⁰.

Cornerstones of “helpful” models are transparency, replicability, and validity.

Therefore, Pfizer recommend that the aim of sharing the disease model with manufactures ICER is not just to enhance transparency but also to:

- Contrast how the ICER models differ from the manufacturer models
- Understand the determinants of potential differences
- Evaluate key sensible variables
- Appraise the stability of the model under various scenarios
- Make appropriate changes based upon feedback

By sharing the economics models with manufacturers, ICER can enhance both transparency, replicability, and validity by engaging in a discussion with the manufactures to identify the best alternative means to address uncertainty in the model structure and inputs.

To achieve the transparency and validity objectives, it is important that ICER also engage with clinical experts in that specific disease area during the design phase of the disease model. The basis of a strong value assessment lies in its foundation. It is very important that the model structure, population selection, comparators, and disease pathway consider as closely as possible clinical guidelines on disease progression and patients’ journey. It is common practice for manufacturers when designing a new model to have advisory boards with key clinical experts and patients to design the most appropriate model structure given the nature of disease, patient perspectives, and clinical guidelines.

Pfizer’s recommendation is to host an open meeting and invite clinical experts and patients in that disease area as panelists to discuss the model structure before asking for stakeholders’ inputs. Different disease model structures, beyond Markov models, should be considered to fully capture the nature of the disease, treatment pathway and overall patient’s journey.

¹⁰ Box, G.E.P. (1979). *Robustness in the strategy of scientific model building in Robustness in Statistics*. In: Launer, R. L. and Wilson, G.N. (Eds). Academic Press.

Moreover, since there is uncertainty in many of the inputs and assumptions used in any model, ICER should run substantial sensitivity analyses and appropriately flag the variables that are most uncertain and may bias the results. Given the changing nature of the transformative medicines being developed and brought to patients by the biopharma industry today, uncertainty in the value of innovative care may be validated only by developing value-based agreements at launch and using more broadly RWE.

4. Inclusion of RWE to fully understand the value of medicines to patients and society

A strong value assessment starts with a strong clinical evaluation. Therefore, we encourage ICER to look at the totality of the evidence and to provide clear guidelines on how **RWE** can be used to complement and/or supplement RCTs in various therapeutic areas.

RWE and patient preference studies provide very relevant information for assessing the value of medicines beyond RCTs as they answer different questions. RWE provides evidence of not whether a medicine is safe and efficacious in a well-controlled and restricted setting, but whether it is safe and effective when prescribed and used in normal daily life by a more heterogeneous population. RWE is an important complement to clinical trial data that helps us better understand how a product's performance evolves in the healthcare system with implications on value and population health. The FDA has initiated guidance on incorporating RWE for regulatory decision making. In the future, more medicines will be launched with more innovative evidence pathways (e.g. basket trials, historic control arms, and RWE). It is unclear how ICER will adapt its value assessment to include innovative evidence pathways and open the door to a fair assessment of RWE and patient preference studies. We appreciate the complexity of trying to manage different levels of evidence and study designs for different therapies (particularly when a review includes a mix of already approved and not yet approved drugs). However, this does not preclude ICER from providing at a minimum a model that incorporates RWE to establish the impact on the value of the drugs where that data exists.

RWE can also provide solutions to address limitations in the QALYs approach, by measuring willingness to pay and patient adherence and persistence to therapy. Willingness to pay data could provide insight into appropriate thresholds for VBP. Real world adherence and persistence data could also more accurately capture patient preferences than adherence from a clinical trial.

Thus, Pfizer recommends that ICER publicly state on how RWE will be included in the clinical effectiveness and cost-effectiveness assessment to fully include the totality of evidence.

5. Rationale for removing budget impact assessment from the value assessment

Finally, Pfizer would like to comment on the inclusion of the budget impact analysis (BIA) in the overall ICER value assessment. Pfizer agrees with the ISPOR BIA Guidelines II that ‘BIA is a means of synthesizing available knowledge at the time of a coverage or formulary listing decision to estimate the likely financial consequences of that decision for a health care system. Given the systems’ highly local nature and decision makers’ varying perspectives, a BIA cannot give a single estimate applicable to all decision makers....Thus, the outcomes of the BIA should reflect scenarios consisting of specific assumptions and data inputs of interest to the decision maker rather than a normative “base” case intended to be generally applicable.’”

Value assessment and formulary listing decision-making are two separate activities. Value assessment considers the efficient, equitable, and high-quality allocation of health care resources at the population level. Value assessment should consider the overall health care spending (including devices, physician and hospital services) and not focus only on medicines to identify optimal efficiency and cost savings in the system. As emphasized by the ISPOR Task Force on US Value Assessment Frameworks, “focusing at the margin on new technologies may ignore or downplay waste and inefficiency in the existing system and in an important sense penalizes new technologies” (Neumann et al.¹¹).

Formulary listing decision-making is mostly linked to meeting affordability and improving patients’ health in a specific health care plan and cannot be generalized to the overall population given the complexity of the US health care system. Pharmaceutical companies are already developing flexible and customer-modifiable BIA to discuss formulary decision making with insurers and IDNs.

Moreover, the affordability budget threshold used by ICER is arbitrary, not scientifically validated, and is not aligned with any affordability challenge faced by insurers in the US.

Additional clarity and rationale on why ICER would continue to include a BIA in their value assessment when this is not helpful to any payer for making formulary decisions would be valuable.

Pfizer’s recommendation is to remove the BIA from the value assessment and instead reinforce the clinical effectiveness and cost-effectiveness assessment for medicines and beyond to look at the overall efficiency and equality of access to health care in the US.

We appreciate this opportunity to provide input to ICER’s 2020 Value Assessment Framework. Value is not a unidimensional concept, and we hope that ICER will incorporate comments from insurers,

¹¹ Neumann et al. (2018). *A Health Economics Approach to US Value Assessment Frameworks—Introduction: An ISPOR Special Task Force Report. Value in Health*, vol. 21, no. 2, pp. 119-123.

hospitals, IDNs, manufacturers, and most importantly patients to advance the 2020 Framework to enhance the validity of the value assessment.

Sincerely,

A handwritten signature in black ink, appearing to read "Cristina Masseria", followed by a horizontal line.

Cristina Masseria, MSc PhD
Methods & Capabilities Lead, PHI
Pfizer Inc. 235 E. 42nd street, New York, NY 10017
Tel. 212 733 5377
Cell. 917 208 9845

June 10, 2019
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, Massachusetts 02109

Re: Call for Public Input on ICER Value Framework

To Whom It May Concern:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to respond to the Institute for Clinical and Economic Review's (ICER) open call for stakeholder feedback on how it can improve its value assessment framework. PhRMA is a voluntary, non-profit organization representing the nation's leading research-based pharmaceutical and biotechnology companies which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives.

PhRMA is also a long-standing supporter of evidence to support health care decision-making, including value assessment frameworks. Advancing better evidence and tools to support sound health care decision-making, including support for advancing the science and use of value assessment frameworks, is a core principle adopted by our members and is central to our policy agenda.^{1,2}

We appreciate ICER taking steps to open its value framework to public comment. Over the past several years, ICER has taken several steps to improve its value framework that align closely with past input PhRMA has provided. For example, we appreciate ICER taking steps towards improved transparency of its models for manufacturers.

However, we believe that ICER can further improve its methods, its process, and the structure of its framework by addressing the full range of recommendations provided by PhRMA and other stakeholders. ICER has received feedback on individual assessments expressing significant concern in several areas, including, but not limited to the premature timing of ICER's analyses, shortcomings of cost-per-quality adjusted life year (QALY) based cost effectiveness analysis (CEA), and the lack of disease-specific clinical expertise on ICER's voting panel.

Because of these and other flaws, ICER's framework continues to pose a significant risk of being misused in ways that have unintended negative consequences for patients and does not provide a sound basis for supporting health care decision making or driving forward a value-based health care system.

We urge ICER to continue to improve its framework, including exploring entirely novel methods of value assessment. As outlined below, it is clear that traditional, QALY-based CEA is fundamentally misaligned with the United States' competitive, complex and pluralistic system, and when used in isolation cannot meet the needs of today's stakeholders or 21st century science. While QALY estimates

¹ PhRMA. "Policy Solutions: Delivering Innovative Treatments to Patients." Available at: <http://phrma-docs.phrma.org/sites/default/files/policy-solutions.pdf>

² PhRMA Value Collaborative. More information available at: <http://www.phrma.org/advocacy/the-value-collaborative>

may provide useful insight to a limited subset of decision makers, they should not set the rule for single pricing or policy decisions, which has the invariable effect of obscuring the important issues identified above.

In addition to moving beyond traditional, QALY-based value assessment, there are several key steps that PhRMA believes ICER must take to establish a methodologically rigorous, patient-centered value framework that can effectively support decision-making by stakeholders:

- I. Actively promote alternative approaches to value assessment, such as multi-criteria decision analysis (MCDA), and reject traditional, QALY-based CEA.
- II. Expand assessments and results to reflect all relevant patient-centered outcomes and relevant patient subgroups based on clinical needs and preferences.
- III. Remove the arbitrary and subjective budget threshold.
- IV. Take a holistic perspective on value that reflects the full range of health care services and interventions and allocate a proportionate share of reviews to other health care services.
- V. Meaningfully integrate clinicians and stakeholders with disease-specific expertise into the value assessment process.

We appreciate ICER's consideration of our recommendations. PhRMA believes that, if these recommendations are adopted and ICER's revised framework is fully validated, it could play a positive role in the movement towards better value in health care. We provide more detail below as to specific concerns, as well as steps that ICER can and should take to address them.

I. Actively promote alternative approaches to value assessment, such as multi-criteria decision analysis, and reject traditional, QALY-based CEA.

It is now recognized by many stakeholders and researchers that traditional methods of QALY-based value assessment are controversial and outmoded. From thought leaders in the field of health economics, to leaders of industry, to patient advocates, many have commented on the shortcomings of QALY-based cost effectiveness in general, and the inappropriateness of their application in the U.S. health care system in particular. ICER itself has acknowledged the concerns expressed by stakeholders and the flaws in QALYs³ and yet persists in generating value-based prices based on QALYs, and similarly flawed metrics.

ICER's reliance on QALYs is highly problematic because they simply do not reflect the reality of treating patients in today's health care system. While the QALY, which provides a single number summarizing the "value" of a treatment, is a commonly used metric for quantifying health benefits, patients do not receive treatments in isolation; the provision of health care is a complicated, multifaceted process with patients receiving care along an entire continuum – from diagnostic testing, clinician consultation, disease management and monitoring, to medication therapy and occasionally hospitalization. The impact, value, and outcomes of each of these services may rely on steps taken before or after, as well as circumstances unique to each patient – including factors such as existence of

³ ICER. The QALY: Rewarding the Care That Most Improves Patients' Lives. December 2018. Available at: https://icer-review.org/wp-content/uploads/2018/12/QALY_evLYG_FINAL.pdf

preferences, comorbid conditions and care seeking behavior.⁴ As noted in a recent paper, it is extraordinarily difficult to translate QALY-based assessments into real-world decision-making in clinically appropriate, patient-centered ways.⁵

In the call for input on its value framework, ICER also sought feedback on the cost effectiveness thresholds used to establish its value-based prices. This question itself, and attempts to objectively answer it, illustrates the inherent flaw of the cost per QALY threshold. If inquiring as to how high or low the thresholds should be set, ICER is simply asking the wrong question. Just as the QALY cannot adequately capture the many aspects of value and wide heterogeneity of patient preferences, a cost effectiveness threshold is not reflective of the intricate reality of the U.S. health care system. And while we acknowledge that our health care system is complex, and involves many perspectives and stakeholders, at its nexus is the patient and provider, who are, and should continue to be ultimately responsible for treatment decisions. Insurers can play a role in guiding treatment options based on formulary coverage and placement, but coverage decisions vary by payer due to differences in enrollee population and willingness to pay. Fundamentally, an approach that relies on a single or several thresholds is incompatible with a system built on patient-centered, individualized treatment decision-making and which comprises hundreds of individual payers with diverse needs and attributes.

The evLYG is not an acceptable supplement or replacement for the QALY.

ICER, clearly aware of the controversy surrounding QALYs, announced a new metric for quantifying value, the equal-value life year gained (evLYG). While we appreciate ICER's acknowledgement that the QALY is inherently discriminatory and problematic, the evLYG does not serve as an appropriate supplement or replacement for the QALY. While attempting to address one issue with the QALY, the discrimination due to discounting utilities for individuals with disabilities, ICER has created several more.

The limitations of the evLYG are clear. For example, when using the evLYG, medicines for conditions that do not reduce life expectancy, like a treatment for eczema or a cure for blindness, would have no value to the health care system. Additionally, the evLYG would value two medicines, one that reduces side effects and one that does not, as equal value. Neither the QALY nor the evLYG properly capture the value of a medicine to patients and people with disabilities. Americans should not be forced to choose between discrimination and capturing quality of life in value assessments. Such a conflict simply highlights the fact that traditional cost-effectiveness assessments cannot possibly serve as an appropriate tool for guiding health care decisions and resource allocation.

⁴ Valderas JM, Starfield B, Sibbald B, et al. "Defining Comorbidity: Implications for Understanding Health and Health Services," *Ann Fam Med*, vol. 7, no. 4, pp. 357-363, 2009.

⁵ Sawhney TG, Pyenson B, Buzby E. "The utility of ICER reports for private payer drug coverage decision-making: Cost-effectiveness assessments." Milliman. September 19, 2018. Available at: <http://www.milliman.com/insight/2018/The-utility-of-ICER-reports-for-private-payer-drug-coverage-decision-making-Cost-effectiveness-assessments/>

ICER should explore new methods of value assessment, such as multi criteria decision analysis.

In their report on value assessment, the ISPOR Special Task Force on U.S. Value Assessment Frameworks strongly recommended that stakeholders explore novel methods of value assessment.⁶ Since then, numerous thought-leaders and organizations have invested resources into the development of transformative, patient-centered forms of value assessment. This includes the PhRMA Foundation, which recently issued a challenge to stakeholders to develop transformative, non-QALY methods of value assessment.⁷ The Foundation received more than 20 responses and plans to publish several of the papers later this year.

For example, the University of Colorado, which already has a strong working relationship with ICER, has established the Pharmaceutical Value initiative (pValue), to test and apply novel methods for value assessment that encourage stakeholder engagement and promote value-based decision making, beginning with MCDA. As they note, “MCDA is particularly helpful in an area like coverage and reimbursement decision-making, where the available alternatives are characterized by multiple, sometimes conflicting, criteria, some of which are judged objectively, some subjectively, and by multiple decision-makers, each with his or her own views on a particular criterion’s relative importance.”⁸ Applying MCDA would allow individual users of ICER’s reports to assign weight to different elements of value, and arrive at their own estimate of a treatment’s worth, which is not currently the case in ICER’s value assessments. It has the potential to make value assessment customizable, transparent and comprehensive, while incorporating other elements of value that patients care about. We recognize that ICER explored use of multi-criteria decision analysis in the past and strongly encourage them to revisit the idea, while simultaneously abandoning traditional CEA.

II. Expand assessments and results to reflect all relevant patient-centered outcomes and relevant patient subgroups based on clinical needs and preferences.

Regardless of the approach ICER takes to value assessment, whether it is QALY-based cost effectiveness analysis, or MCDA, it is imperative that ICER takes a comprehensive, patient-centered perspective on value. ICER should follow the recommendations of thought leaders in the field by expanding their value elements to incorporate other elements of value that matter to both patients and society. It should also ensure that the significant heterogeneity in clinical characteristics and preferences in patients is captured. Our health care system is becoming increasingly patient-driven and personalized, and ICER should strive to capture those characteristics.

Historically, ICER has frequently responded to such critiques by conducting scenario or subgroup analysis that are not reflected in ICER’s results or press releases. This is unacceptable. The vast majority

⁶ ISPOR Special Task Force on U.S. Value Assessment Frameworks. “A Health Economics Approach to US Value Assessment Frameworks—Summary and Recommendations of the ISPOR Special Task Force Report.” Value in Health. February 2018. Available at: [https://www.valueinhealthjournal.com/article/S1098-3015\(17\)33894-9/fulltext](https://www.valueinhealthjournal.com/article/S1098-3015(17)33894-9/fulltext)

⁷ PhRMA Foundation. PhRMA Foundation Issues a Call for Papers to Improve Health Care.” January 31, 2019. Available at: <http://www.phrmafoundation.org/wp-content/uploads/2019/02/News-Release-VA-Challenge-Awards-2019-5.pdf>

⁸ The University of Colorado Pharmaceutical Value. “Complimenting Coverage and Reimbursement Decisions With Multi-Criteria Decision Analysis.” AJMC. May 27, 2019. Available at: <https://www.ajmc.com/contributor/the-university-of-colorado-pharmaceutical-value/2019/05/complimenting-coverage-and-reimbursement-decisions-with-multicriteria-decision-analysis>

of stakeholders do not have time to read the entirety of ICER's reports. Publishing a limited subset of results conveys a sense of certainty and homogeneity that is simply false.

ICER should strive to incorporate all relevant outcomes into its final value-based prices.

The ISPOR Special Task Force also recommends the inclusion of a "a more comprehensive economic evaluation that could include novel elements of value."⁹ Studies have long shown that patients place significant emphasis on outcomes other than prolonged survival or cost, and that these preferences vary considerably depending on factors such as type and severity of disease and individual life circumstances. Payers, the end-user of ICER's reports, have diverse needs and preferences as well. Many individuals and organizations, such as the Innovation and Value Initiative, are developing methods to incorporate these value elements, such as insurance value and option value, quantitatively into health technology assessment, and ICER should leverage their work.

Accounting for all relevant value elements not only further aligns ICER with the needs of patients, but best practices in the field. The First Panel on Cost Effectiveness in Health and Medicine recommended using a societal reference case; this recommendation is now 20 years old, and ICER has still not adopted it. In recognition that most CEAs did not include a true societal perspective, the recent update recommended two base cases, which allowed for the inclusion of the narrower health systems perspective but re-emphasized the importance of the societal perspective.¹⁰

ICER continues to root its value-based prices solely in the payer perspective, which is problematic and diverges from the stated principle of putting patients first, and at the center of the discussion. ICER should consider not only using two base cases for its value assessments but releasing value-based prices based on both perspectives.

ICER often ignores important differences among patient subgroups.

Individual patient differences occur due to many factors, such as genetic variation, differences in comorbidities, and quality-of-life preferences. The Second Panel on Cost-Effectiveness in Health and Medicine agreed and was clear in calling for heterogeneity to be considered through the presentation of subgroup-specific cost-effectiveness ratios. Yet ICER has been slow to recognize heterogeneity, and often fails to release value-based prices for all relevant subgroups, even when it conducts subgroup analyses as part of its assessment. By drawing attention to the average effectiveness of a treatment for an entire patient population, ICER ignores, and encourages payers to ignore, important differences in the clinical needs and preferences of patients. It also puts ICER out of step with the movement towards more personalized health care.

In some circumstances these summarized results are being applied by a decision maker without their full understanding of the modeling, the assumptions, and levels of uncertainty. ICER should consider providing confidence intervals to the reports to reflect the level of uncertainty. In addition, summaries require a more detailed listing/outline of the limitations associated with their derived point estimates.

⁹ Lackdawalla DN, Doshi JA, et al. "Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report." Value in Health. February 2018. Available at: [https://www.valueinhealthjournal.com/article/S1098-3015\(17\)33892-5/abstract](https://www.valueinhealthjournal.com/article/S1098-3015(17)33892-5/abstract)

¹⁰ Neumann PJ, Sanders GD, Russell LB, et al. Cost-Effectiveness in Health and Medicine. Oxford University Press. 2017.

III. Value frameworks should focus on value. ICER should remove the arbitrary and subjective short-term budget threshold from its framework.

ICER's short-term affordability analysis sets a threshold for spending on all new medicines following launch, regardless of the patient population, or health system burden of the condition. ICER's reliance on short-term affordability thresholds runs counter to efforts to achieve truly value-based care. While we appreciate that ICER has taken steps to improve the short-term affordability component of its framework, we continue to believe that ICER should cease estimating short term affordability to avoid serious, unintended consequences for future patients and innovation.

ICER's short-term affordability threshold punishes innovation and could have significant consequences for patient outcomes.

By creating an inverse relationship between the number of FDA approvals per year and the budget impact threshold, ICER is effectively recommending an approach that would punish the biopharmaceutical for developing too many new products. Not only would such a policy disincentivize innovation, it would incentivize and reward low sector output. As Former Assistant Secretary for Planning and Evaluation at Health and Human Services (HHS), Robert Rubin, observed, "If the [ICER] arbitrary budget cap were to be implemented, then new drugs for common diseases like diabetes or congestive heart failure or atherosclerotic cardiovascular disease may be left on the drawing board."¹¹

ICER further penalized innovation by applying their short-term affordability cap only to newly-launched treatments, making no effort to analyze existing spending on health care. This siloed view ignores the fact that better use of medicines impacts other aspects of the health care system, often reducing costs on other services. In fact, the Congressional Budget Office scores policies that increase use of medicines as achieving a 0.2 percent saving on non-drug health costs for each 1 percent increase in the use of drugs. Applying a short-term budget threshold completely disregards this important relationship, a limitation that reinforces silo-based thinking about health care.

The impact on innovation could have serious consequences for patient outcomes – a recent analysis assessed the hypothetical impact of applying ICER's short-term budget impact threshold to Lipitor (atorvastatin) at its launch. If used to limit access to Lipitor, the budget threshold could have resulted in just 28 percent of the 2.9 million people who actually received the treatment having access to atorvastatin in the five years following launch.¹² This limited access in the first five years on the market could have resulted in an estimated 72 thousand additional major vascular events and nearly 19 thousand additional deaths.¹³

ICER argues that spending on treatments and interventions beyond the short-term budget threshold "could displace equally or more valuable care." However, by focusing only on the value of medicines

¹¹ "Value Pricing For Drugs: Whose Value, What Price?" [Health Affairs](#). March 28, 2016

¹² Ortendahl JD, Broder MS, Harmon AL. "Modeling the Mortality Impact of Budget Thresholds." Partnership for Health Analytic Research. ISPOR Poster Presentation. May 2019. Available at: <https://www.ispor.org/heor-resources/presentations-database/presentation/intl2019-1479/89987>

¹³ Ortendahl JD, Broder MS, Harmon AL. "Modeling the Mortality Impact of Budget Thresholds." Partnership for Health Analytic Research. ISPOR Poster Presentation. May 2019. Available at: <https://www.ispor.org/heor-resources/presentations-database/presentation/intl2019-1479/89987>

and disregarding the remaining 86 percent of health care, ICER risks facilitating the exact behavior they state they are attempting to avoid. ICER's dismissal of these concerns, stating the threshold serves as an alert to payers to allow for future planning, does nothing to diminish its potential impact on patient access and outcomes.

The calculation used to determine the annual threshold is arbitrary, highly variable, and dependent on inputs unrelated to value.

ICER relies on a budget impact threshold that is highly dependent on the individual inputs comprising its calculation. Such volatility raises the question of whether it is fit for purpose. For example, in a recent whitepaper on ICER's budget impact threshold, actuaries outlined several technical and conceptual issues that limit its usefulness to private payers, one of which was the arbitrary nature of the calculation, which resulted in dramatic variation year over year.¹⁴ They found that "GDP growth plus 1 percent is not consistent with either historical experience or expected future pharmacy cost growth."¹⁵ Tethering the threshold to highly variable inputs such as GDP growth and the number of FDA approvals results in unpredictable thresholds driven by variables unrelated to the value of a medicine. One study found that applying ICER's methodology to the 1992 to 2012 period resulted in annual thresholds varying from \$1.36 billion in 2004 to *negative* \$607 million in 2009.¹⁶

Each individual input has a dramatic impact on the threshold from year to year. In a recent analysis, Avalere replicated ICER's budget impact threshold analysis, substituting the number of FDA approvals while holding all other variables constant, to quantify the impact of changing a single variable in the calculation. When using the lowest, average, and highest number of FDA approvals over the past 20 years, the recalculation resulted in thresholds of \$1.81 billion, \$1.18 billion, and \$684 million, respectively.¹⁷ Avalere's analysis concluded that as the number of FDA approvals per year increased, the short-term budget threshold, and percentage of patients that could be treated before crossing the threshold, decreased.

IV. Take a holistic perspective on value that reflects the full range of health care services and interventions and allocate a proportionate share of reviews to other health care services.

Medicines are distinct from nearly any other health care service available to patients today. Investment in research and development provides value across the globe in ways that investment in other health care sectors, like building new hospitals and training additional physicians, are unable to achieve. The innovation lifecycle facilitates this global benefit through the use of generics and biosimilars that

¹⁴ Sawhney TG, Pyenson BS, Buzby E. "The utility of ICER reports for private payer budgeting: Budget impact analyses." Milliman. January 2019. Available at: <http://www.milliman.com/insight/2019/The-utility-of-ICER-reports-for-private-payer-budgeting-Budget-impact-analyses/>

¹⁵ Sawhney TG, Pyenson BS, Buzby E. "The utility of ICER reports for private payer budgeting: Budget impact analyses." Milliman. January 2019. Available at: <http://www.milliman.com/insight/2019/The-utility-of-ICER-reports-for-private-payer-budgeting-Budget-impact-analyses/>

¹⁶ Ortendahl JD, Broder MS, Harmon AL. "Modeling the Mortality Impact of Budget Thresholds." Partnership for Health Analytic Research. ISPOR Poster Presentation. May 2019. Available at: <https://www.ispor.org/heor-resources/presentations-database/presentation/intl2019-1479/89987>

¹⁷ Leinwand B, Shah A. "ICER's Use of FDA Approval Volume to Calculate Budget Impact Thresholds: A Scenario Analysis." Avalere. July 2018. Available at: <https://avalere.com/insights/icers-use-of-fda-approval-volume-to-calculate-budget-impact-thresholds-a-scenario-analysis>

prevent unrestricted monopolies while ensuring biopharmaceutical companies can recoup their research and development costs while investing in future innovations.

Due to this lifecycle, over the next 5 years, savings due to the entrants of lower cost competitors following loss of exclusivity for brand medicines will more than offset spending on newly-launched brand medicines over the same period.¹⁸ Despite these unique characteristics of the sector, and the fact that spending on prescription medicine accounts for just 14 percent of total health care costs in the U.S. – half of which (7 percent of total health care) is on brand medicines – ICER’s assessments focus primarily on new brand medicines.^{19, 20}

Because ICER fails to examine all relevant aspects of clinical care and patient management, their assessments cannot effectively guide health care resource allocation decisions.

ICER’s myopic view on medicines is not only unfounded, but undermines their stated mission of driving a “more effective, efficient, and just health care system.”²¹ If ICER was truly dedicated to improving health care and guiding evidence-based resource allocation, assessments would take a holistic view of the health care system, not focus on a sector that accounts for such a small share of total health spending.

Dwarfing the amount spent on medicines, health care inefficiency and waste is estimated to account for more than a quarter of health care spending.²² A multi-stakeholder analysis spearheaded by the American Board of Internal Medicine and AcademyHealth categorized more than 400 common procedures and health care interventions as “low value,” or providing no or minimal benefit to patients. Among the interventions identified, more than 75 percent were non-drug related.²³ Low-value care is a major driver of inefficiency in health care and an untapped opportunity to increase quality and reduce spending.

As ICER’s value framework explains, “waste and inefficiency pose major problems.”²⁴ However ICER’s assessments primarily focus on new medicines, in contrast to their stated intention of not targeting a single group,²⁵ while making no attempt to assess and recommend prices for health care services well known to be of low value.

Dismissing this glaring inconsistency by citing lack of evidence on other health care services comparable to the quality of evidence available for drugs reinforces the disconnect between ICER’s stated mission of ensuring “the United States evolve toward a health care system that provides sustainable access to high-value care for all patients” and their actions.²⁶ Notably, limited evidence for a

¹⁸ IQVIA. “2018 Medicine Use and Spending.” Published May 2019.

¹⁹ Centers for Medicare & Medicaid Services. National Health Expenditures Data.

²⁰ Berkeley Research Group, “The Pharmaceutical Supply Chain: Gross Drug Expenditures Realized by Stakeholders,” January 2017. Available at: <http://www.thinkbrg.com/newsroom-publications-vandervelde-blalock-phrma.html>

²¹ ICER. “About.” Available at: <https://icer-review.org/about/>

²² Institute of Medicines. “Best Care at Lower Cost: The Path to Continuously Learning Health Care in America.” 2012. Available at: <http://www.nationalacademies.org/hmd/Reports/2012/Best-Care-at-Lower-Cost-The-Path-to-Continuously-Learning-Health-Care-in-America.aspx>

²³ American Board of Internal Medicine Foundation. Choosing Wisely. April 2014. Available at: <http://www.choosingwisely.org/>

²⁴ ICER. “Final Value Assessment Framework for 2017-2019.” Available at: <https://icer-review.org/final-vaf-2017-2019/#overview>

²⁵ ICER. “Final Value Assessment Framework for 2017-2019.” Available at: <https://icer-review.org/final-vaf-2017-2019/#overview>

²⁶ ICER. “Final Value Assessment Framework for 2017-2019.” Available at: <https://icer-review.org/final-vaf-2017-2019/#overview>

specific medicine does not hinder ICER's ability to carry out assessments and assign value-based prices in those cases.


ICER's singular focus on medicines is the proverbial man looking for his keys under the lamp post. The newest innovations with the most robust evidence supporting their efficacy are often the easiest for payers to target and restrict access. However, if the goal is to improve efficiency, affordability, and health system sustainability, while ensuring patients have access to the most innovative treatments, a holistic perspective is critical.

V. Meaningfully integrate clinicians and other stakeholders with disease-specific expertise into the value assessment process.

PhRMA appreciates ICER's recent efforts to further engage with stakeholders. That said, we remain concerned that ICER is not fully integrating patients and other critical stakeholders into the value assessment process. ICER must ensure that individuals participating in the value assessment process, particularly clinical experts, have disease-specific experience and expertise. ICER should publish the process and necessary qualifications for participation in the appraisal committees, as well as other committees and boards that govern and advise ICER. Once ICER selects individuals to participate in committees, those individuals' qualifications and experience should be made public. At a minimum, clinical experts should have specific clinical expertise within the relevant disease area, and have experience interacting with patients who suffer from the illness or condition.

PhRMA and ICER have a mutual interest in the development of sound, patient-centered decision support tools. We appreciate ICER's engagement with our industry in the revision of its value framework, and hope that you consider incorporating our feedback as the framework evolves.

Sincerely,

A handwritten signature in blue ink, appearing to read "Randy Burkholder", with a stylized, flowing script.

Randy Burkholder
Vice President, Policy & Research

A handwritten signature in blue ink, appearing to read "Lauren A. Neves", with a stylized, flowing script.

Lauren A. Neves
Senior Director, Policy & Research

June 5, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review

RE: Value Assessment Framework

Dear Dr. Pearson,

Integrating ICER assessments more directly into the formulary evaluation process of Premera's P&T Committee helped us improve the quality of our value assessments. We reported initial results of this project led by pharmacy resident Emily Tsiao in a panel session at the AMCP Annual Meeting in March 2019.¹

Collaboration with ICER is natural for us. Premera's Value Matrix, developed in 2010 as part of our Value-Based Formulary project,^{2,3} precedes ICER's Value Framework and incorporates many of the same additional factors along with the net clinical benefit and cost-effectiveness, providing a more comprehensive picture of the complexities that must be considered when making coverage decisions in today's world. We also appreciate ICER's two-dimensional evidence grading rubric, which considers the effect size of a treatment on one axis and our confidence in the estimate on the other. These factors are interconnected, with the probability of a false positive result decreasing as the reported effect size increases.

ICER public meetings provide a multi-stakeholder venue where these complex issues can be laid out in the context of a specific coverage decision. This provides input from patients and patient advocacy groups that we would otherwise not hear. The meetings and technology assessment reports add value to Premera's formulary process.

Sincerely,



John Watkins, PharmD, MPH, BCPS
Formulary System Manager

REFERENCES:

1. Tsiao E, Watkins J, Pearson S. Using ICER Reports to Supplement Limited Drug Approval Information. Presented at AMCP Annual Meeting, San Diego, CA, March 27, 2019.
2. Sullivan SD, Yeung K, Vogeler C, et al. Design, implementation, and first-year outcomes of a value-based drug formulary. *JMCP* 2015 Apr;21(4):269-75.
3. Yeung K, Basu A, Hansen R, Watkins J, Sullivan S. Impact of a Value-based Formulary on Medication Utilization, Health Services Utilization, and Expenditures. *Med Care*. 2017 Feb;55(2):191-198.
4. Yeung K, Tsiao E, Watkins J. Redesigning a Value-Based Formulary to Address Current Pharmaceutical Spending Trends: Changes in Drug-Tier Classifications. *JMCP*. 2019 Mar;25(3a):S92.

June 10, 2019

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

Submitted Electronically: publiccomments@icer-review.org

RE: 2020 Update to ICER Value Framework

Dear Dr. Pearson,
Recordati Rare Diseases Inc. (RRD) is pleased to submit its response to the Institute for Clinical and Economic Review's (ICER's) national call for input on updating and refining its value assessment framework.

RRD is a biopharmaceutical company committed to the research, development, and commercialization of high-impact therapies for devastating rare diseases. RRD works in close alliance with the rare disease patient advocacy communities to increase awareness, improve diagnosis, and enhance availability of treatments for individuals with rare diseases.

RRD recognizes that the pace of innovation in understanding and treating catastrophic medical conditions creates a new set of uncertainties for US health care systems. We support ICER's stated goal of helping to "inform policy that will ensure truly transformative treatments are rewarded handsomely, while neither patients nor society pays too much for care that doesn't offer patients significant benefit"¹

While 95% of the approximately 7,000 rare diseases identified to date remain without an FDA-approved treatment or cure, the rare disease treatments developed in the 35 years since enactment of the Orphan Drug Act have benefited countless patients and demonstrated real-world impact on both patient outcomes and treatment costs. RRD's Panhematin®, for example, was approved as the first orphan drug, and remains the gold standard for treating acute porphyria attacks. We expect that the acute porphyrias will, with potential approval of givosiran, developed by Alnylam Pharmaceuticals, become one of the very few extremely rare diseases with more than one treatment option. Our comments are offered to guide ICER's approach to reviewing new treatments for extremely rare diseases that, like acute porphyria, have an existing treatment with robust real-world data on both improved outcomes and cost-effectiveness.

¹ https://icer-review.org/wp-content/uploads/2018/12/QALY_evLYG_FINAL.pdf

We urge ICER to:

- Incorporate real-world data, including retrospective studies utilizing claims data, to benchmark annual costs of treating a disease with and without an established treatment, and assess the cost-effectiveness of that treatment;
- Consider an expanded or flexible panel composition to include one or more clinicians with recognized expertise in treating a specific rare or extremely rare disease, as well as a patient representative impacted by the disease;
- Recognize that, for extremely rare diseases, a new market entry is unlikely to replace an existing product. Manufacturers may not be able to sustain production of necessary therapies if both the volume and payment are reduced;
- Provide stakeholders with adequate notice of an impending review to enable meaningful participation in model development, identification of patient preferences on outcomes, and disease-specific quality of life indicators that could be relied upon in calculating value.

Background: Acute Porphyria and Panhematin®

The porphyrias are very rare metabolic disorders caused by altered activities of enzymes within the heme biosynthetic pathway, usually due to an inherited mutation in the gene for that enzyme. Heme is essential in the function of hemoglobin and many other hemoproteins, including hepatic enzymes. The liver is the major source of overproduction of heme pathway intermediates in patients with hepatic porphyrias such as acute intermittent porphyria. Intermittent attacks are due to elevated levels of these intermediates and their neurotoxic effects on the central, peripheral, autonomic, and enteric nervous systems.

Patients experiencing an acute porphyria attack are almost always in severe, intractable pain when they present to the emergency room, and most are vomiting and suffer from dehydration. Sensory and motor neuropathy is also common, and can include pain in the extremities, patchy numbness, paresthesias, and dysesthesias. Motor weakness usually starts in the upper extremities and may progress to the lower extremities and, with prolonged attacks, may involve cranial nerves and lead to bulbar paralysis, respiratory impairment, and death. Some patients with prolonged attacks experience advanced motor neuropathy with quadriplegia and respiratory paralysis. Prolonged attacks should be avoided through prompt hemin administration. Patients with prolonged attacks who are eventually treated appropriately with intravenous hemin regain function over a gradual recovery period, although many find that some level of paralysis remains long after a prolonged attack.

Acute porphyria attacks are progressive and present a serious medical emergency requiring prompt attention. The goal of therapy for an acute attack is to abate the attack as rapidly as possible with intravenous administration of hemin. Panhematin® is the only treatment available to treat these attacks, and it may take a facility a day to order and receive Panhematin®. During

this time, inpatient care by a multidisciplinary team is needed to provide appropriate supportive and symptomatic care until the acute attack resolves.

Even facilities with substantial expertise in porphyria treatment see few patients for admission each year – estimated at between 6 and 10 annual admissions in such facilities. These hospitals will, unless patients present with a very mild attack, or are in the earliest “prodromal” phases of an attack, admit patients and administer Panhematin® as quickly as possible. It is also essential to provide supportive care for attack symptoms, including intravenous pain management (opioids are required), fluids and electrolytes, and intravenous glucose until Panhematin® is available, and to monitor respiratory function until the attack abates.

Due to the inpatient prospective payment system relied upon by most public and private payers, mining data on porphyria admissions to assess Panhematin®-associated outcomes can be challenging. The diagnosis related group (DRG) for the acute porphyrias is a catch-all category of rare metabolic disorders that ultimately results in significant financial loss to facilities providing standard-of-care treatment for an acute porphyria attack. Unfortunately, not all acute porphyria admissions capture the improved outcomes associated with Panhematin® due to the combination of a clear and significant financial downside with a failure to appreciate the potentially catastrophic consequences of delaying Panhematin® infusions.

RRD urges ICER to incorporate real-world data, including retrospective studies utilizing claims data, to benchmark annual costs of treating a disease with and without an established treatment, and assess the cost-effectiveness of that treatment.

RRD understands ICER’s preference for randomized controlled clinical trial data in its assessments of new and established treatment options. Unfortunately, ICER’s standard of excellence identified in its review of Spinal Muscular Atrophy (SMA) therapies is not attainable for all disease states, much less for extremely rare diseases such as the porphyrias. Porphyria patients more often than not encounter long journeys to even achieve an accurate diagnosis. Although the American Porphyria Foundation has compiled a patient registry, that registry was not sufficiently established and robust to support clinical trial enrollment until long after Panhematin® approval made randomized studies all but impossible from an Investigational Review Board (IRB) perspective.

We also believe that even the most carefully controlled clinical trial can fail to capture the bottom line information ICER seeks to communicate to health care stakeholders – whether product use improves both outcomes and associated costs in a particular disease state. Appropriate use of real-world data can be a powerful tool to enable ICER to assess whether a new product for treating a rare disease represents a significant benefit to patients, and the economic value of any added benefit. RRD recently sought to estimate the annual healthcare utilization and expenditures for acute porphyria patients treated with Panhematin® using real-world health care claims data accessed through MarketScan.

Analysis of 10 years of claims data (2007-2017) demonstrated that acute porphyria patients treated with Panhematin® experienced real-world annualized total costs for porphyria-related care at less than half that of non-real-world estimates reported in the literature. We believe that use of this type of analysis, particularly when an existing treatment has a long track record of integration into the standard of care, would improve ICER's ability to estimate the value of new treatments by establishing a more reliable benchmark for overall disease-related care costs.

We are happy to share our methodology and results with ICER.

RRD asks that ICER consider an expanded or flexible panel composition to include one or more clinicians with recognized expertise in treating a specific rare or extremely rare disease, as well as a patient representative impacted by the disease.

RRD notes that ICER relies upon a subset of outside entities to inform and/or develop the models utilized in reviews of new and existing products, yet the panel convened to review its findings and make recommendations remains fixed regardless of the disease state. We agree that a "core" panel enables ICER to rely upon a set of committed stakeholders and experts, but believe that disease-specific expertise is essential for meaningful panel deliberations and well-informed decisions. Relying on ICER's relatively short timeframes for stakeholder input may be sufficient when reviewing relatively common disease states. Rare diseases, however, can present unique challenges that may not be resolved by relying on experts and patients to submit page-limited discussions within an exceedingly short timeframe.

The National Institutes of Health (NIH) has established a Rare Disease Research Clinical Network (RDRCN) with currently consisting of 22 distinct clinical research consortia and a Data Management and Coordinating Center (DMCC). Each consortium focuses on at least three related rare diseases, participates in multisite studies and actively involves patient advocacy groups as research partners. The DMCC enables uniform high-quality data collection and analysis and facilitates information sharing across the network.

The Porphyrrias Consortium within the RDRCN, for example, brings together porphyria experts at six academic institutions, the American Porphyria Foundation and biopharmaceutical companies interested in improving diagnosis or developing new treatments for these diverse diseases. When a specific rare disease treatment falls within the purview of one of the RDRCN consortia, we urge ICER to reach out to the relevant consortium and afford the opportunity for panel inclusion of at least one consortia clinician and one patient representative. Early outreach to consortia will also enable ICER to incorporate input from these experts into scoping documents, model development or identification, panel questions, and analysis of evidence.

RRD similarly expects that including disease-specific patient panel members could enable ICER to reframe how it positions the patient and caregiver in deciding whether a treatment increases quality of life. A common critique of ICER use of quality adjusted life years (QALY) in its

reviews is that it neglects the simple, yet important question of what patients, suffering with a specific disease, value. Patients and their caregivers play pivotal roles in encouraging innovation, increasing disease awareness, and even in developing patient registries. Leaving this voice out of the value equation dilutes the validity of ICER's work and could have the unintended impact of negating their hard work by constricting access to the treatments they have relied upon or hoped for.

ICER should recognize and account for the fact that, for extremely rare diseases, a new market entry is unlikely to replace an existing product.

Evaluating two treatment alternatives for an extremely rare disease presents challenges for both ICER and any stakeholder seeking to rely on its assessment. A spokesperson for Biogen, the manufacturer of Spinraza noted in response to ICER's recent report that:

As the report notes, there is a significant difference in robustness and quality of evidence for Spinraza as compared to Zolgensma. The analysis, however, fails to account for those differences. **Spinraza is the standard of care in SMA and has benefitted the lives of more than 6,600 people.** In contrast, Zolgensma is an experimental therapy which has reported results to date for only 15 patients followed for up to 2.5 years, seven of whom are reported to have subsequently initiated treatment with Spinraza,²

RRD believes that, as detailed above, ICER's evaluation of multiple treatments in a rare disease state should account for accumulated evidence, including real-world evidence, associated with an established standard of care. Like Spinraza, Panhematin® is the standard of care, but its track record of safely and effectively treating acute porphyria patients spans over three and a half decades, rather than a few years. Similarly, even if givosiran were to demonstrate remarkable value for the money, its market entry will not eliminate the need for Panhematin® to address porphyria patients who are not candidates for the treatment as well as for breakthrough attacks in givosiran-treated patients.

ICER should provide stakeholders with adequate notice of an impending review to enable meaningful participation in model development, identification of patient preferences on outcomes, and disease-specific quality of life indicators that could be relied upon in calculating value.

RRD urges ICER to prioritize patient and caregiver engagement. Chronic rare diseases like porphyria are often poorly understood, and their impact on patient lives cannot be easily captured in terms of life years lost or gained, or quality of life indicators designed for the general

² <https://endpts.com/to-be-cost-effective-biogen-should-slash-spinraza-price-and-novartis-cannot-justify-a-4m-5m-price-tag-for-zolgensma-icer/>

population. Meaningful, disease-specific treatment impacts, such as alleviation of symptoms or the ability to be productive in work or home settings, often are not reflected by global or specific clinical measures that feed into a QALY.

Although ICER discusses outreach to patients and patient groups as part of its inquiry, this outreach often does not start until the process is well underway, and ICER has drafted a scoping document for which a 3-week time period is allowed for public comments. Not only should patient representation on the panel include disease-specific patients or caregivers, but patient and caregiver stakeholders should be proactively brought into the process to inform the scoping document, inform the model, and identify outcomes that are of substantial importance. Similarly, the 3-week time is far too short if ICER hopes to have patient perspectives inform the resulting analysis.

Conclusion

RRD appreciates ICER's public outreach and the opportunity to comment on the proposed framework adaptation. If you have any questions or would like to discuss our comments and recommendations, please contact Paul Stickler at 847-205-5503.

Sincerely,

Michael Waters
General Manager, Recordati Rare Diseases

Regeneron Pharmaceuticals welcomes the opportunity to provide feedback to the Institute for Clinical and Economic Review's (ICER) and recommends the following two changes to its 2020 value assessment framework.

1. In case of unfavorable value assessment in the base case, ICER should aim to identify whether plausible patient subgroups exist where the drug does constitute good value

The majority of ICER's assessments to date have found that the assessed product's estimated net price exceeds its value-based price and, therefore, conclude that the drug is overpriced within the the scope of the indication. Specific methodological challenges aside, we believe that a simple binary assessment of a drug's value into two mutually exclusive categories of fairly priced vs. too expensive may not be the only useful output from an ICER report to inform formulary decision makers in the US.

In addition to the typical cost-effectiveness assessment and determination of a drug's value-based price based on a given cost/QALY threshold, we would like to propose a third domain of relevant outputs. Instead of answering the question whether a drug is cost-effective or not, that third domain would aim to identify and evaluate patient subgroups in which the drug is likely to be cost-effective at an estimated net price. This approach would be applicable for only those assessments where the drug was found not to be cost-effective in the base case in the studied indication.

Virtually all patient populations assessed in prior ICER evaluations are heterogenous in nature. Patients vary by socio-demographic characteristics, but also by clinical characteristics. Most importantly, there is variation with respect to the parameters that directly affect either, or both, the numerator or the denominator of the cost-effectiveness ratio. The simplest example is disease severity: cost-effectiveness assessments typically yield ICERs that are more favorable among those patient subgroups that are sicker at baseline because these patients have more to gain from effective treatments. However, there are multiple other relevant parameters. For example, drugs indicated for life-threatening therapies may derive a greater benefit for younger patients by virtue of the fact that they have more life years left to gain. This patient heterogeneity is currently disregarded in the ICER framework, which draws conclusions about the value of a medicine for the average patient, thereby ignoring the possibility that subgroups of patients may exist where this medicine may very well be a worthwhile use of scarce healthcare dollars.

Health technology assessment bodies outside the US have long adopted this logic into their assessments. A recent review of 847 recommendations made by NICE's technology appraisal committees published since the organizations inception finds that exactly 200 of these recommendations, or almost 25%, have received an "optimised recommendation", which is defined as reimbursement "recommended for a smaller subgroup of patients than originally stated by the marketing authorization" (NICE 2019).

Further, we appreciate that investigating patient subgroups within the context of a cost-effectiveness model does introduce the possibility of chance findings, meaning, the ICER estimate may be below an acceptable threshold for a given subgroup, but such a finding might be driven by, say, exceptionally

good efficacy of a drug in a given subgroup that was merely observed by chance. However, in our view, such a possibility is not a sufficient reason to dismiss the proposed patient subgroup approach outright. As briefly discussed above, in many instances, there are biologically plausible relationships that directly affect either the costs or QALYs. Potentially influential and biologically plausible subgroups can be identified prospectively in collaboration with clinical experts. Adding this straight-forward step to provide a more refined evaluation of drug cost-effectiveness will substantially enhance the utility of ICER evaluations for formulary decision makers in the US and follows a precedent that has already been set by NICE and other HTA agencies.

Thus, for those assessments where a drug is considered not cost-effective in the base case, we recommend that in its revised framework, ICER should follow the lead of other agencies and also report whether biologically plausible patient subgroups exist where this drug is likely to be cost-effective and where patient access should not be restricted.

2. Raising the willingness to pay threshold above \$150k/QALY gained, particularly for end-of-life therapies

The current ICER framework uses a willingness to pay threshold of \$100k and \$150k per QALY gained, which is increased to \$50k to \$500k for drugs targeting ultra-orphan diseases. However, neither the original thresholds nor the wider ones have theoretical or empirical basis.

There is consensus in the literature about the arbitrary nature of the lower value (\$50,000), mentioning its “curious resilience” (Neumann et al. 2014). It is commonly thought to be based on a historical value of the cost of one year of dialysis. However, a more recent re-analysis on the actual cost per QALY gained associated with dialysis therapy pegged this estimate at \$129,090 (Lee et al. 2009). Adjusting for medical care inflation since the publication of this study would generate a cost per QALY gained around \$172,000 in 2019 dollars. However, a medical CPI adjusted cost/QALY threshold that is based on the cost of dialysis may still generate relatively conservative values. In the relevant literature, even higher threshold values have been proposed. The commonly cited three times the GDP per capita as proposed by the World Health Organization would yield approximately \$178,600 per QALY (based on 2017 GDP per capita estimates). Threshold values as high as \$428,286 per QALY have been proposed, depending on the methods used and assumptions made (Hirth et al. 2008, Braithwaite et al. 2008, Neumann et al. 2014, Marseille et al. 2015).

The thresholds also focus on the average gain, while the value of the average gain can be different depending on the spread of the gain. A US study found that for example in cancer, patients tend to place more value on a larger gain for a smaller portion of the patient population, rather than an average gain for most of the population (Lakdawalla 2012). This led the authors to conclude that patients diagnosed with life threatening diseases may disproportionately value the tail end of the survival curve. All else equal, therapies that offer the hope for a cure are likely to be preferred to those that do not, even if the chance of a cure is small and the expected mean survival is the same. Thus, it appears that in the context of end-of-life therapies, there may exist a special set of considerations that may not exist in the typical

cost-effectiveness assessment. Specifically, a QALY gained by someone with a terminal condition and a very short life expectancy may inherently be more valuable than a QALY gained by someone with a condition that merely affects quality of life.

Acknowledging the special circumstances involved in evaluating drugs aimed at end of life treatments, NICE has adopted a set of rules that allow drugs to be reimbursed using a substantially higher willingness to pay threshold of £50,000 per QALY instead of the commonly used £20,000 - £30,000 range if very specific end-of-life criteria are met (NICE 2009). It seems reasonable that such considerations also be reflected in the revised ICER value framework.

Thus, we recommend that in its revised framework, ICER considers the following key points:

- (1) replace the current \$100k-\$150k threshold range with a single point estimate of \$175k that is in line with the medical CPI inflated cost of dialysis estimate and, also in line with the three times per capita GDP recommendation by the WHO; and**
- (2) allow for a higher threshold to be applied, particularly for end-of-life treatments. The specific definition of an end-of-life treatment could be adopted from the NICE definition, but it could also be customized for the US setting. In those special circumstances, we recommend that ICER use a significantly higher threshold than \$175k, such as \$250k or even \$300k.**

Sincerely,

Vera Mastey
Executive Director
Health Economics and Outcomes Research

References

Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the \$50,000 per quality-adjusted life-year decision rule? *Med Care*. 2008 Apr;46(4):349-56.

Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making*. 2000 Jul-Sep;20(3):332-42.

Lakdawalla DN, Romley JA, Sanchez Y, Maclean JR, Penrod JR, Philipson T. How cancer patients value hope and the implications for cost-effectiveness assessments of high-cost cancer therapies. *Health Affairs*. 2012 Apr 1;31(4):676-82.

Lee CP, Chertow GM, Zenios SA. An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. *Value Health*. 2009 Jan-Feb;12(1):80-7.

Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. *Bull World Health Organ*. 2015 Feb 1;93(2):118-24.

National Institute for Health and Care Excellence. Technology appraisal data: appraisal recommendations. <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data/appraisal-recommendations> Accessed May 13th, 2019.

National Institute for Health and Care Excellence. Appraising life-extending, end of life treatments. <https://www.nice.org.uk/guidance/gid-tag387/documents/appraising-life-extending-end-of-life-treatments-paper2> Accessed May 13th, 2019.

Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the \$50,000-per-QALY threshold. *N Engl J Med*. 2014 Aug 28;371(9):796-7.

Re: Open Input on ICER 2020 Value Assessment Framework

publiccomments@icer-review.org

Thursday, June 6, 2019

The following observations I have made since 2014 while following assessments ICER has conducted on a variety of different therapies and while a voting panel member since the Spring of 2017 on the CTAF group.

I have observed on several occasions while participating in industry sponsored patient advocacy meetings and reading several Op Ed articles in California media about some basic misunderstandings regarding the function ICER serves together with how the assessment framework and process of the meetings is applied.

The calculations regarding the Equal Value of Life Years Gained (evLYG) and Quality-Adjusted Life Years (QALY) are not easily understood by lay patient advocates or consider in the context of the framework assessment process and all the components unless they have studied the basics and observed the application of the meetings and their relevance to the expert evaluation data, evidence, and clinical data gathered over the ca.9 month period need to generate a final report from start to finish. Science is a moving target, evolving to embrace the therapeutic benefit of the patient. What people have difficulty understanding then becomes mysterious and can be perceived as harmful. The process is a complicated one due to the considerable coordination need to gather data and input and the number of components plus the variety of stakeholders that can be involved in some way.

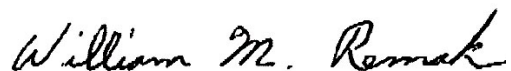
My strongest recommendation is more about translating into non-technical terminology the framework for the public to understand and perhaps using illustrations, graphics, animation and example to better engage a better understanding of the process and the reports. It is a

complicated activity and very inclusive of multiple viewpoints with real world data that has a real and perceived relevance to the topic being addressed. The administration and organization required to carry the monumental task of putting the ICER framework to bare with each issue evaluated is masterfully done and seemingly under-appreciated by the stakeholders that have the most to gain from this work.

The principles used have taken decades to develop and are constantly being refined to improve these assessments by many organizations in the field that conduct activities that perform and use these kinds of evaluations around the world. Technology Assessments as a science has been evolving for well over four decades. It will continue to evolve.

I commend ICER for making the commitment to find ways to perfect the framework while remain inclusive and impartial to bring together the wisdom and analytical magic that reflects a sound scientifically based reasoning regarding the clinical effectiveness and best analysis of costs for a healthier population affected by these issues and our society as a whole. I have seen first-hand the benefits in better outcomes and affordability and numerous other ways ICER reports have received well regarded impact. Additionally, they give inspiration to innovators to do better and reach for cures, perhaps the unintended consequence of finding out the truth.

Respectfully,

A handwritten signature in black ink that reads "William M. Remak". The script is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

William (Bill) M. Remak, B. Sc.MT. B. Public Health, SGNA, AHCJ, ASCO
149 Wyndham Way, Ste. 223
Petaluma, Ca 94954



June 10, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: “Institute for Clinical and Economic Review (ICER) Seeks Public Input for 2020 Value Assessment Framework”

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson,

Sanofi is pleased to provide comments to the Institute for Clinical and Economic Review’s (ICER) request for open input on the planned update of its value assessment framework (VAF)¹.

We share ICER’s goal of sustainable access to high-value care for all patients. We commit to supporting optimal value assessment of our therapies by generating relevant evidence on multiple dimensions of value to meet the needs of all key stakeholders, including patients, healthcare providers, and payers. This holistic approach guides our evidence generation planning for therapies in development and across the product life course and is embedded in our US Pricing Principles². We employ a broad-based internal value assessment process that includes exhaustive review of existing evidence on unmet needs and available treatment options and extensive consultation with external stakeholders. We assess and weight available evidence, evaluate patient populations and sub-groups most likely to benefit from novel candidates, identify key clinical, patient-relevant and economic outcomes, and consider potential impacts of therapies on treatment paradigms and relevant societal/contextual factors.

We appreciate ICER’s ongoing willingness to engage on their VAF, as evidenced through previous consultations and evolution of their framework. It is in this spirit that we share our current views on how to ensure the VAF keeps pace with the purpose for which it is intended.

Our recommendations to ensure ICER leverages best practice in value assessment are as follows:

- Clarify the purpose and intended use of the VAF.
- Strengthen patient engagement and input and formal integration of patient-focused outcomes and contextual factors.

- Embrace a holistic conceptualization of value that fully incorporates important novel elements in a unified framework for value assessment.
- Include a societal perspective reference case analysis in all evidence reviews, formalizing co-equal consideration of healthcare sector and societal perspectives.
- Adopt new modeling approaches to aggregate multiple dimensions of value and integrate competing stakeholder preferences in value assessments, such as augmented CEA (ACEA) or multi-method approaches.
- Update the current evidence rating matrix and net health benefit assessment process to ensure it is fit for purpose for the rapidly evolving therapeutic landscape and findings are replicable.
- Adapt or eliminate the use of uniform cost-effectiveness thresholds (CETs), reflecting their limited applicability for the diverse, pluralistic US healthcare system and cutting edge therapies.
- Clarify the limitations regarding the applicability of budget impact assessments conducted for individual payers, and eliminate the narrowly focused affordability threshold in the VAF.

1. Clarify the purpose and intended use of the VAF.

We share ICER's commitment to the importance of rigorous evidence-based value assessment of healthcare interventions. However, ICER's overview³ of the current VAF still lacks a clear acknowledgement of the distinctions between its role as an evidence evaluator and that of the healthcare decision maker. ICER should explicitly frame and delimit its responsibility as an evidence assessor and acknowledge the limitations of its reviews for informing coverage and reimbursement decisions on specific populations. Health care coverage decisions should not be determined by the results from a single value assessment. This principle is especially salient when considering relevance for the large, diverse, pluralistic US healthcare system. It is critical for ICER to provide greater transparency and clarity on this issue in its VAF and evidence reviews, especially as the organization seeks to grow and serve as an objective intermediary between stakeholders in promoting value-based healthcare.

Thus, we strongly encourage ICER to state categorically in its VAF that ICER views its role as an evidence evaluator focused on evidence review and evidence assessment, and distinct from deliberative responsibilities of the decision maker. Evidence reviews should be clearly labeled for their intended uses and consistently include the following elements:

1. Explicit characterization of uncertainty and alternative viable interpretations.
2. Recognition of heterogeneity within populations and disease states.
3. Input from all stakeholders, especially including patients and caregivers, and evaluation of elements to account for quality of life, burden to caregivers, return to work/productivity and other patient-centric values.

4. Broad representation of potential benefits and disadvantages, comprehensive health care costs and potential offsets.
5. Reliance on high quality, validated evidence and evidence synthesis procedures and reliable, transparent models.

2. Strengthen patient engagement and input and formal integration of patient-focused outcomes and contextual factors.

We recognize that ICER has increased its efforts to solicit input from patients and include patient factors in its deliberations. However, we are concerned that significant additional progress is still needed on this front. Recent empirical research suggests that patient input is still least likely to be incorporated among stakeholders who respond to ICER's evidence review protocols. For example, a recent analysis of ICER's response to feedback received from stakeholders concluded that comments from patient advocates, focused on the adequacy of existing evidence, patient perspectives and transparency, were least likely to be acknowledged and addressed (15.9% vs. 32% overall)⁴.

We urge ICER to do more to integrate patients and patient advocates in all phases of its evidence reviews, from scoping discussions to final panel debates on the conclusions of evidence reports. This is critical in general, but given even more significance as ICER increases its engagement and executes reviews of treatments for rare or ultra-rare conditions and other highly specialized treatments. Generalized quality-of-life measures used in cost-effectiveness analyses are inadequate to represent the patient perspective in rare disease, and disease-specific measures are typically required. As noted above, standard cost-effectiveness analyses also rarely incorporate caregiver and societal impacts of new therapies, which are highly prominent in rare conditions.

ICER has a significant opportunity to lead in formalizing patient engagement and input in value assessment, and we recommend this as a renewed focus of its 2020 VAF update. We encourage ICER to engage consistently and align its efforts with other patient advocacy organizations such as the National Health Council (NHC) and the Community Oncology Alliance (COA), as well as patient-focused research organizations such as the Patient-Centered Outcomes Research Institute (PCORI).

PCORI requires that investigators engage patients and other healthcare stakeholders integrally in the research process. Forsythe and colleagues⁵ recently reviewed the early findings from such sponsored studies, demonstrating that patients and other stakeholders can be successfully engaged as both consultants and collaborators in designing studies, determining study endpoints, tailoring interventions to target critical needs and preferences of patients, and enrolling participants. Such approaches must be systematically incorporated into drug development and evidence generation planning, but also formally integrated into the value assessment process for new therapies.

A second ambitious effort to incorporate patient preferences in data collection to inform value assessment is the Patient Perspective Value Framework (PPVF)⁶, an ongoing collaboration between FasterCures (a center of the Milken Institute) and Avalere. The PPVF is a phased initiative that seeks to apply and ensure the integration of five major domains of patient information in existing value frameworks: patient preferences; patient-centered outcomes; patient and family costs;

assessment of the quality and applicability of evidence; and evaluation of the usability and transparency of materials. This initiative seeks to embed patient concerns as criteria in existing evidence appraisal methods, thus generating more personalized value assessments. The initiative's first phase developed a high-level framework, and ongoing work encourages routine collection of patient-relevant data to inform net health benefit scores and includes specific proposals to evolve existing VAFs to include patient preferences systematically. Again, we recommend that ICER align its patient engagement efforts with this and similar initiatives.

Substantial progress is also ongoing in directly incorporating patient-informed value elements for disease states in economic evaluations, and we recommend that ICER pursue such approaches in planned updates to its VAF. For example, Slejko, Gray, and colleagues have recently aligned COPD outcomes with patient-informed value elements in economic evaluations, using stated preference methods to derive quantitative results for patient preferences^{7;8}.

3. Embrace a holistic conceptualization of value that fully incorporates important novel elements in a unified framework for value assessment.

We reiterate our prior recommendation that ICER adopt a comprehensive conceptualization of value in its statement of the purpose and principles of the VAF^{9;10;11}. Value assessments should include a broad, diverse array of factors important to the stakeholders in healthcare. In the development of its current VAF ICER made progress in soliciting greater patient and provider input and recognizing potential extra-clinical patient benefits and societal level contextual considerations. However, these and other important value elements, typically unmeasured or evaluated in traditional cost/QALY approaches, are still treated qualitatively and selectively in ICER's evidence assessments. This ignores a rapidly expanding literature on both the important contributions of these elements to the value of therapies and the advent of formal procedures to incorporate them in evidence assessments.

It is well-recognized that the QALY captures only a subset of potential benefits resulting from healthcare treatments, and QALY-based approaches have many other limitations in application^{12;13;14}. In the interim since ICER's last update to its VAF, significant advances have been made in identifying, measuring, and quantifying the impact of so-called novel elements of value that better represent societal and patient level preferences and potential benefits of healthcare interventions. The ISPOR Special Task Force (STF) report by Lakdawalla et al¹⁵ presents an extended discussion of such novel elements, including the value of hope, insurance value, severity of disease, real option value, equity, and scientific spillovers. Moreover, the STF report describes the mathematical underpinning for measuring these dimensions and procedures and formally incorporating them in value assessments in addition to QALYs, net costs, and other commonly recognized factors such as productivity and adherence-improving attributes¹⁶.

Emerging empirical research also confirms the significant magnitude of the impact of such factors on overall value^{17;18;19}. For example, findings suggest that insurance value may account for as much as 40-60% of the conventional value of morbidity improvements, patients express a willingness to pay approximately \$35,000 for each one year increase in the standard deviation of potential survival, and real option value contributes significant percentages to the net monetized benefit of

treatments of breast cancer and other disease states²⁰. The importance of these factors may be crucial when considering the impacts of specialized therapies, for example ultra-rare disease therapies and “curative” therapies. We urge ICER to develop a fully unified value assessment framework that incorporates these elements.

We have three additional comments related to the conceptualization and purpose of ICER’s current VAF.

First, the construct of Equal Value of Life Years Gained (evLYG)²¹ recently introduced by ICER is not a solution for the broader limitations of the QALY. We recognize ICER’s intent to address potential concerns with discriminative effects of the QALY on older patients and those with severe illness and disabilities. However, we strongly disagree that this measure, which simply represents an estimate of life years gained, is an advance and potential solution to the identified limitations of the QALY. The evLYG is not a new concept or advance, and in fact reinstates disadvantages that the QALY was designed to address. As Cohen et al²² point out, the evLYG fails to credit the value of therapies that improve symptoms and quality of life, in addition to extending survival. The evLYG may also negatively affect cost-effectiveness analysis findings, especially for conditions such as mental illness, chronic back pain, and dermatologic disease which severely impact quality of life but may not reduce life expectancy. Given these limitations, the evLYG is primarily useful only as an adjunct sensitivity measure.

Second, we reiterate our previous comment that ICER’s VAF should promote balanced evaluation of all types of healthcare interventions, not just medications. This is a stated objective of the VAF, but lags in practice, as ICER’s evidence reviews are overwhelmingly focused on drug assessments. Given that medications comprise at most 16% of overall US healthcare spending²³, this disproportionate focus is unwarranted and undercuts ICER’s efficacy in encouraging high-value care. This is a lost opportunity for ICER. A broader focus on assessing healthcare interventions, consistently applied, would benefit society as a whole.

Finally, we urge ICER to expand and give more explicit consideration in its VAF and evidence reviews to identifying existing low-value care that may be appropriate for assessment. Greater attention will promote improved processes of care and support accommodation for high-value innovation^{24;25}.

4. Include a societal perspective reference case analysis in all evidence reviews, formalizing co-equal consideration of healthcare sector and societal perspectives.

ICER’s current VAF continues to give sole primacy to the healthcare system perspective. While important, this restriction significantly undercuts attention to other critical participants in the healthcare system. We strongly recommend that ICER’s VAF also require that all evidence reviews report a Reference Case analysis based on a societal perspective and utilize an Impact Inventory checklist, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine²⁶ and others²⁷.

We appreciate that ICER has previously incorporated societal perspectives in limited circumstances, i.e., its value framework for ultra-rare disease therapies²⁸, but this expectation should be generalized to the overall framework. This approach will also facilitate the incorporation of novel elements of value, as discussed above, which are primarily aligned to the societal perspective. Diversifying its formal consideration of perspective in value assessment to incorporate societal interests will also serve ICER's ambition to serve as an intermediary in value-based discussions with a broad-based constituency of participants in healthcare.

5. Adopt new modeling approaches to aggregate multiple dimensions of value and integrate competing stakeholder preferences in value assessments, such as augmented CEA (ACEA) or multi-method approaches.

ICER's continued reliance in its current VAF on traditional health technology assessment methods centered on the QALY ignores widespread agreement on the limitations of this approach in reflecting a multidimensional concept of value and incorporating competing stakeholder perspectives. These limitations are also amplified in the emerging therapeutic landscape that includes personalized, often curative therapies, and rare or ultra-rare disease targets.

Therefore, we also urge ICER to investigate and consider incorporating new methods to aggregate multiple elements of value and differing stakeholder perspectives that enable explicit consideration of tradeoffs across attributes. Augmented cost-effectiveness analysis (ACEA) methods, which seek to combine disparate components of value into a single metric, are very promising. Lakdawalla and Phelps²⁹, for example, build a framework that computes the value of treatments as the combination of the traditional value of QALYs gained, net of costs, plus previously ignored terms for insurance value and the value of hope, accounting for the effect of risk preferences. Other practical approaches to ACEA were recently discussed at the 2019 ISPOR US meeting^{30; 31; 32; 33}.

ACEA approaches have limitations in incorporating some value considerations within the CEA framework, including issues of scientific spillover effects and evaluating patients with multiple chronic conditions³⁴. Thus, we also recommend that ICER renew its consideration of multi-method approaches to represent and aggregate multiple differing stakeholder perspectives. One such approach for continued consideration is multi-criteria decision making (MCDA), because this family of modeling procedures offers the promise of transparently and formally incorporating multiple disparate value considerations. We recognize that concerns have frequently been raised about the complexity and practicality of MCDA approaches, but ongoing focused efforts show promise for resolving these problems³⁵. Recent modeling initiatives for value assessment of treatments for Rheumatoid Arthritis³⁶ and Non-Small Cell Lung Cancer³⁷ demonstrate the feasibility of such integrated approaches. Evolving ICER's VAF to accommodate these more comprehensive approaches value assessment is a significant leadership opportunity for the organization.

6. Update the current evidence rating matrix and net health benefit assessment process to ensure it is fit for purpose for the rapidly evolving therapeutic landscape and findings are replicable.

We also encourage ICER to update its current evidence matrix³⁸ to improve the reproducibility of evidence ratings, expand incorporation of real world evidence (RWE), formalize processes for early engagement and scientific dialogue with stakeholders and new evidence updates (NEUs), and adapt procedures to accommodate novel innovations such as curative therapies.

ICER's current procedures for estimating the magnitude of comparative benefit, judging uncertainty, and summarizing net health benefit are notably qualitative and informal in nature. This approach may give a false impression of precision and limit the reproducibility and generalizability of findings. We urge ICER to evaluate more formal, explicit approaches to quantifying net health benefit that will facilitate transparency and reproducibility. ICER should review and consider adapting approaches used in alternative settings. For example, Raju and colleagues³⁹ and Coplan et al⁴⁰ propose semi-quantitative benefit-risk analyses for drugs to inform value assessment, which may be helpful to review and consider opportunities for adaptation.

Substantive inclusion of real-world evidence (RWE) in the evidence matrix is a second important opportunity, because evidence derived from clinical practice is critical to obtain a full picture of the value of the intervention. We appreciate ICER's recognition that incorporating RWE is important to accurately measuring an intervention's full value, but currently RWE is tangentially considered in most reviews, if at all, and there is no formal iterative process outlined in the evidence rating matrix to update value assessments as salient evidence on value accumulates after product approval. ICER itself has proposed a framework to guide the use of RWE in evidence assessments, and there is an opportunity to operationalize this or alternative approaches in its VAF update⁴¹. With the increasing adoption of RWE in clinical development, regulatory approvals, and life cycle management processes, it is imperative that ICER also address this issue in its current plans for updating its VAF. We also encourage ICER to review its reliance on classical evidence hierarchies such as GRADE or other conventional approaches in its evidence matrix, because many such frameworks are of limited utility for the evaluation of observational research. We encourage ICER to incorporate quality standards for RWE assessment, such as ISPOR-ISPE's Special Task Force recommendations on this topic⁴².

We also recommend that ICER develop an enhanced, dynamic value assessment framework to reflect the evolution of increasing evidence over the lifecycle of therapies. First, ICER should consider appropriate opportunities to support early scientific dialogue processes for discussions with innovators, patient representatives and other relevant stakeholders. This may facilitate the development of early consensus on key elements relevant to later value assessments. After marketing approval, we suggest that ICER develop a more formalized, inclusive framework for initiating and conducting new evidence updates (NEUs), which it has indicated is a growing priority for future reviews. Our experience of the NEU process to date is that these reviews are much less transparently begun and executed than standard evidence assessments, limiting opportunities for fruitful interactions and input by stakeholders.

Finally, it is apparent that the current evidence rating matrix is also primarily designed for a healthcare system in which therapeutic innovation is principally incremental in nature and uncertainties are substantial. Such conventional concepts of incremental benefit and uncertainty in treatment response are challenged by the advent of therapies that deliver cures or dramatic life year

gains, and targeted treatments based on genetic status. Clinical development and licensing processes are also rapidly evolving to accommodate accelerated or conditional approvals, and so also have significant implications for the future timing and methods employed in current value assessments^{43;44}.

7. Adapt or eliminate the use of uniform cost-effectiveness thresholds (CETs), reflecting their limited applicability for the diverse, pluralistic US healthcare system and cutting edge therapies.

ICER also requested comment on the cost-effectiveness thresholds (CETs) it uses to establish value-based price benchmarks for treatments.

First, we reiterate our prior comment that the use of a single ICER is inappropriate for the heterogeneous, pluralistic U.S. healthcare system and limited in applicability, as the value for money assessment is inherently local in nature. Willingness to pay for any given individual payer is driven by a multitude of factors specific to the plan and population, and the application of a single set of CETs is not appropriate for the diverse therapeutic areas under evaluation. Thus, for individual payers, whether or not a therapeutic option falls within a particular CET is largely unrelated to decision making and adds little to the conversation on value at the population level. The recent report by Pyenson et al.⁴⁵ provide a detailed examination of the difficulties in aligning national level assessments based on cost/QALY approaches and CETs to the highly localized circumstances and decision requirements of U.S. commercial payers. Difficulties are also encountered in applications of national level CETs to public payer settings. For example, a recent study by Xcenda⁴⁶ modeled the application of ICER-like cost-effectiveness standards in Medicaid, concluding that major treatment access limitations could result for conditions including multiple myeloma, multiple sclerosis, non-small cell lung cancer, rheumatoid arthritis, and psoriasis.

We also continue to disagree with ICER's decision to include a \$50,000 per QALY lower threshold for its evidence reviews. This is inappropriate for U.S. application. If ICER persists in setting cost-effectiveness thresholds, we recommend that ICER revisit alternative methodological approaches to establishing CETs, for example, value of a statistical life approaches, or other methods deriving from welfare economics theory and consensus-based approaches^{26;47}. We also recommend that ICER review potential adjustments in thresholds for disease severity. Sweden, for example, adjusts thresholds according to "need", which is directly related to disease severity⁴⁸.

We recognize that ICER has shown willingness to adapt CETs for specific categories of treatments and patient populations, notably in the case of therapies for ultra-rare conditions⁴⁹. Although ICER has discussed a CET range of a maximum of \$500,000 per QALY, we continue to be concerned that this threshold is not reflective of orphan drugs in practice. Moreover, ICER has continued to advocate use of the base-case value-based price for such therapies at a CET of \$150,000 per QALY gained, which again is not representative of typical practice. A 2015 review of published cost-effectiveness analyses for approved ultra-rare treatments in the US and EU concluded that the median base case incremental cost-effectiveness ratio was \$591,200/QALY, with the median estimate in the sensitivity analyses of \$1,958,674/QALY⁵⁰. We also reiterate that the limitations of using formal cost-effectiveness analyses for orphan drugs are widely recognized, and urge ICER to

revisit its current procedures for these and other categories of specialized treatments such as gene therapies in its planned update of the VAF⁵¹.

We also reiterate our continuing concerns with ICER's approach to determining qualification criteria for ultra-rare disease treatments and recommend that this be revised in the VAF update. We previously commented¹¹ that the prevalence threshold of <10,000 patients for "ultra-rare" conditions used by ICER lacks scientific validity and creates the impression of false precision and a sharp division between the prevalence of rare conditions. This cutoff excludes many conditions that are traditionally considered at the very low end of the spectrum for rare disease definitions, including Acute Myeloid Leukemia (ca.15,000), Hemophilia (ca. 20,000), and Cystic Fibrosis (ca. 30,000). As a result, there is the potential to disadvantage the value assessment of therapies for rare conditions with only marginally different prevalence. We strongly urge ICER to develop a more flexible assessment approach to treatments for these rare conditions. We also encourage ICER to revisit its criterion that therapies represent a "major gain in improved quality of life and/or length of life." We continue to be concerned that this definition is vague, and that there is no consensus on what constitutes a "major gain". If such a criterion is used, it is important that more explicit definitional attributes be developed.

8. Clarify the limitations regarding the applicability of budget impact assessments conducted for individual payers and eliminate the narrowly focused affordability threshold in the VAF.

ICER's decision to separate long-term value for money and short-term affordability and potential budget impact in the final conceptual structure for its current VAF addressed a number of prior concerns. However, ICER's continued engagement in evaluating short-term affordability and budget impacts is outside the scope of ICER's core value assessment mission, and we urge ICER to re-evaluate this position in its VAF update and educate on the limitations of applying national budget impact assessments to local conditions. Budget impact assessment is not value assessment, and budget impact assessment should be the province of the budget holder rather than evidence evaluators.

Budget impact assessment is inherently local in nature and specific to patient population characteristics and plan benefit designs. Given this, national assessments such as ICER's irrelevant to budget holders for their decision making, and in fact may be misinterpreted and unintentionally limit patients' access to therapies and affect health outcomes. Inaccurate assessments can also have chilling impacts on innovation priorities. We recognize that ICER has been responsive to prior critique on the issue of budget impact assessment and made positive changes to its BIM methodology in its current value framework, but we continue to have concerns that the application of access and affordability alerts and the decision to retain an artificial budget impact threshold for innovation may have misleading effects.

The recent report by Snider and colleagues⁵¹ in *Value in Health* illustrates the challenges of accurately forecasting and interpreting real-world budget impacts for both new and existing products. Reviewing budget impact models (BIMs) reported by ICER prior to 2016, the authors compared outputs for aggregate therapy cost and therapy uptake, and compared these estimates against real-world estimates derived from actual drug sales data. The results indicated striking

upward deviations between ICER's BIM estimates and real-world estimates for both forecasted studies and those that relied on contemporaneous current market estimates for products already on the market. For example, ICER's study estimates of unmanaged uptake exceeded actual real-world uptake by an average of 25-fold, with values varying from 7.4 to 54. ICER's aggregate cost estimates also exceeded real-world estimates by 36-fold on average (range 9 to 85). These comparisons may have been influenced by ICER's assumption of "unmanaged uptake", later removed from its current approach. However, substantial variation was also observed for studies of contemporaneous estimates of already marketed products, in which both estimates reflect managed uptake. These estimates also differed by an average factor of 7.6 for uptake estimates and 8.6 for aggregate treatment costs for ICER's values versus those derived from real-world estimates.

Reviewing potential reasons for the discrepancy, the authors discuss the possibility of an "ICER effect", in which the disclosure of ICER's reports depresses real-world drug uptake as payers respond by implementing formulary policies intended to reduce access to the reviewed drugs. There is a risk that such actions, if present, would be based on flawed estimates of budget impact for products, and that patients' access might be prematurely limited prior to a full understanding of the benefits of products. Recently presented research by Ortendahl et al.⁵² highlights this possibility. The authors model the effects of a hypothetical counterfactual scenario in which ICER's short-term budget impact threshold was applied to atorvastatin at its launch in 1997. Results suggest that this scenario would have resulted in precluding access to atorvastatin to 72 percent of the patients who actually received the therapy in the first five years after approval, with a resulting potential significant negative impact on both vascular events and mortality attributable to hyperlipidemia.

The risk of significant misinterpretation by users of budget impact assessment findings persists, given ICER's decision to continue to calculate a questionable national annual budget impact threshold for prescription drug therapies, and to utilize this as a basis for its affordability and access alerts. This calculation is narrowly focused on drug expenditures rather than all investments in the health care system, making it an incomplete tool to assess trade-offs and contribute meaningfully to affordability considerations. The use of such blunt instruments at the societal level, using potentially flawed assumptions, does not do justice to the nuances of budget impact evaluation in patient populations and plans in our large, pluralistic health care system. We urge ICER to eliminate this approach and focus on the challenges of value assessment rather than budget evaluation.

We thank ICER for soliciting input on the planned update of its value assessment framework, and hope that you consider our recommendations. We are happy to engage in additional dialogue on these issues or otherwise assist at any time.

Yours Sincerely,



Bryan M. Johnstone, Ph.D.
Health Economics & Value Assessment, External Affairs
Sanofi

References:

1. Institute for Clinical and Economic Review seeks public input for 2020 value assessment framework. <https://icer-review.org/announcements/icer-seeks-public-input-for-2020-value-assessment-framework/>, May 1, 2019. Accessed May 27, 2019.
2. Sanofi. U.S. Pricing Principles, 2019. https://www.sanofi.us/-/media/Project/One-Sanofi-Web/Websites/North-America/Sanofi-US/Home/corporateresponsibility/Prescription_Medicine_Pricing_2019.pdf. Accessed June 5, 2019.
3. Institute for Clinical and Economic Review. Overview of the ICER value assessment framework and update for 2017-2019. <https://icer-review.org/wp-content/uploads/2018/03/ICER-value-assessment-framework-update-FINAL-062217.pdf> Accessed May 20, 2019.
4. Xcenda (AmerisourceBergen) and PIPC. Responding to stakeholder input: finding the patient voice in ICER's value assessments. September 2018. http://www.pipcpatients.org/uploads/1/2/9/0/12902828/pipc_xcenda_icer_stakeholder_mapping_final_report_2018__003_.pdf. Accessed May 20, 2019.
5. Forsythe LP, Carman KL, Szydlowski V, et al. Patient engagement in research: early findings from the Patient-Centered Outcomes Research Institute. *Health Affairs* 2019; 38:3: 359-367.
6. FasterCures. Patient Perspective Value Framework. 2019. <https://www.fastercures.org/programs/patients-count/patient-perspective-value-framework/>. Accessed June 5, 2019.
7. Slejko JF, Gray C, Hong Y, Rueda JD, Zhang C, dosReis S. ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.
8. Gray C, Slejko JF. Identifying COPD patient-informed value elements in economic evaluations: a systematic review. ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.
9. Sanofi. Comments to ICER, "ICER Opens National Call for Proposed Improvements to its Value Assessment Framework" Submitted September 12, 2016.
10. Sanofi. Comments to ICER, "Overview of the ICER value framework and proposals for an update for 2017-2018". Submitted April 3, 2017.
11. Sanofi. Comments to ICER, "Proposed value assessment framework for treatments that represent a potential major advance for serious ultra-rare conditions". Submitted September 22, 2017.
12. Neumann PJ, Willke RJ, Garrison LP. A health economics approach to US value assessment frameworks – introduction: an ISPOR Special Task Force report [1]. *Value in Health* 2018;119-123.
13. Pettitt DA, Raza S, Naughton B, et al. The limitations of QALY: a literature review. *Journal of Stem Cell Research and Therapy*. 2016; 6(4). <http://dx.doi.org/10.4172/2157-7633.1000334>.

14. Neumann PJ, Cohen JT. QALYs in 2018 – advantages and concerns. *Journal of the American Medical Association* 2018; 319(24):2473-2474.
15. Lakdawalla DN, Doshi JA, Garrison LP, et al. Defining elements of value in health care – a health economics approach: an ISPOR Special Task Force report [3]. *Value in Health* 21 2018; 21: 131-139.
16. Lakdawalla DN, Doshi JA, Garrison LP, et al. Technical appendix. Referenced in Defining elements of value in health care – a health economics approach [3]: an ISPOR Special Task Force report. *Value in Health* 21 2018; 21:131-139.
17. Lin PJ, D'Cruz B, Leech AA, et al. Family and caregiver spillover effects in cost-utility analyses of Alzheimer's disease interventions. *Pharmacoeconomics*. 2019; 37(4):597-608.
18. Jacobs JC, Van Houtven CH, Tanielian T, Ramchand R. Economic spillover effects of intensive unpaid caregiving. *Pharmacoeconomics*. 2019; 37(4):553-562.
19. Incerti D. From theory to practice: making value assessment more flexible and comprehensive. ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.
20. Kamal-Bahl S. Considering novel concepts of value from a manufacturer's perspective. ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.
21. Institute for Clinical and Economic Review. The QALY: rewarding the care that most improves patients' lives. December 2018. https://icer-review.org/wp-content/uploads/2018/12/QALY_evLYG_FINAL.pdf. Accessed June 5, 2019.
22. Cohen JT, Ollendorf DA, Neumann PJ. Will ICER's response to attacks on the QALY quiet the critics? Center for the Evaluation of Value and Risk in Health. <https://cevr.tuftsmedicalcenter.org/news/2018/will-icers-response-to-attacks-on-the-qaly-quiet-the-critics>. Accessed June 5, 2019.
23. Kleinrock MA, Westrich MA, Buelt L, Aitken M, Dubois RW. Reconciling the seemingly irreconcilable: how much are we spending on drugs? *Value in Health* 2019; <https://doi.org/10.1016/j.jval.2018.11.009>. Accessed June 5, 2019.
24. Fendrick AM, George D. The drug price iceberg: more than meets the eye. *The American Journal of Managed Care* 2019; 25, 2: 294-205.
25. Choosing Wisely. <https://www.choosingwisely.org/>. Accessed June 5, 2019.
26. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Cost effectiveness in health and medicine. 2nd Ed. New York, NY: Oxford University Learning; 2017.
27. Drummond MF, Schwartz JS, Jonsson B, et al. Key principles for the conduct of HTA for resource allocation decisions. *International Journal of Technology Assessment in Health Care* 2008; 24, 3: 244-258.
28. Institute for Clinical and Economic Review. Modifications to the ICER value assessment framework for treatments for ultra-rare diseases. <https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf>. Accessed June 5, 2019.
29. Lakdawalla DN and Phelps CE Evaluation of medical technologies with uncertain benefits. (Working Paper). University of Southern California, 2019.

30. Neumann PJ. Can we make global value assessments more flexible and comprehensive? ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.
31. Drummond M. Considering novel concepts of value within a decision-making framework. ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.
32. Towse A. The case for weighted/augmented CEA. ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.
33. Lakdawalla D. Getting the science right on novel value elements. ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.
34. Phelps CE. Multi-criteria decision analysis (MCDA) vs. augmented cost-effectiveness analysis (ACEA). ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.
35. Phelps CE, Madhavan G. Valuing health: evolution, revolution, resistance, and reform. *Value in Health* 2019;22,5:505-510.
36. Incerti D, Curtis JR, Shafrin J, Lakdawalla DN, Jansen JP. A flexible open-source model for value assessment of biologic treatment for rheumatoid arthritis. *Pharmacoeconomics*, published online 09 February 2019. <https://doi.org/10.1007/s40273-018-00765-2>. Accessed June 5, 2019.
37. Innovation and Value Initiative. IVI-NSCLC Value Model. January 31, 2019. <https://www.thevalueinitiative.org/ivi-nsclc-value-model/>. Accessed June 5, 2019.
38. Ollendorf DA, Pearson SD, Institute for Economic and Clinical Review. ICER Evidence Rating Matrix: A User's Guide. Updated: July 18, 2017. <http://icer-review.org/wp-content/uploads/2016/02/Rating-Matrix-User-Guide-UPDATED-06.30.17.pdf>. Accessed June 5, 2019.
39. Raju GK, Gurumurthi K, Domike R. Benefit-risk analysis for decision-making: an approach. *Clinical Pharmacology & Therapeutics* 2016; 100,6: 654-671.
40. Coplan PM, Noel RA, Levitan BS, et al. Development of a framework for enhancing the transparency, reproducibility and communication of the benefit-risk balance of medicines. *Clinical Pharmacology & Therapeutics* 2011; 89: 312-315.
41. Hampson G, Towse A, Dreitlein B, et al. Real world evidence for coverage decisions: opportunities and challenges. ICER White Paper, March 2018. <https://icer-review.org/wp-content/uploads/2018/03/ICER-Real-World-Evidence-White-Paper-03282018.pdf>. Accessed June 5, 2019.
42. Berger ML, Sox H, Willke RJ et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the Joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Value in Health* 2017;20:1003-1008.
43. Eichler H-G, Barker R, Bedlington N, Bouvy JC, Broekmans AW, Bucsics A, Cerreta F, Corriol-Rohou S, Granados A, Le Cam Y, Shurman A. The evolution of adaptiveness: balancing speed and evidence. *Nature Reviews Drug Discovery* 2018 17:845–846 (2018) <https://www.nature.com/articles/nrd.2018.90>

44. Facey K, Granados A, Guyatt G, Kent A, Shah N, van der Wild GJ. Generating health technology assessment evidence for rare diseases. *International Journal of Technology Assessment in Health Care*, 2014;30,4:1-7.
45. Pyenson B, Sawhney TG, Buzby E. The utility of ICER reports for private payer drug coverage decision-making: cost-effectiveness assessments. New York, NY: Milliman, Inc. September 19, 2018.
46. Xcenda. Impact analysis of ICER formulary implementation in Medicaid. https://www.xcenda.com/-/media/assets/xcenda/english/content-assets/white-papers-issue-briefs-studies-pdf/icer-medicaid-analysis_march-2019.pdf?la=en&hash=03590A12822FB95144692F0BF6FFF846E2E26F1A. Accessed May 20, 2019.
47. Arjunji R. How much should we – and can we – pay for gene therapies? ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.
48. Persson U. Value-based pricing in Sweden: lessons for design? White paper, Office of Health Economics. November 2012. <https://www.ohe.org/publications/value-based-pricing-sweden-lessons-design>. Accessed June 5, 2019.
49. Institute for Clinical and Economic Review. Institute for Clinical and Economic Review. Modifications to the ICER value assessment framework for treatments for ultra-rare diseases . <https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf>. Accessed June 5, 2019.
50. Aggarwal S, Topalogu H, Kumar S. Systematic review of cost effectiveness of ultra-orphan therapies. *Value in Health* 2015, 18:7: A533.
51. Garrison LP, Jackson T, Paul D et al. Value-based pricing for emerging gene therapies: the economic case for a higher cost-effectiveness threshold. *Journal of Managed Care & Specialty Pharmacy*, February 2019, <https://www.jmcp.org/doi/10.18553/jmcp.2019.18378>.
52. Snider JT, Sussell J, Tebeka MG, et al., Challenges with forecasting budget impact: a case study of six ICER reports. *Value in Health* 2019: 332-339.
53. Ortendahl JD, Broder MS, Harmon AL. Modeling the mortality impact of budget thresholds. Partnership for Health Analytic Research. ISPOR Annual Meeting, May 18-22, 2019, New Orleans, LA, USA.

Board of Directors**Executive Committee**

Amy M. Miller, PhD
President and CEO
Society for Women's Health Research

Roberta L. Gartside, MD
Board Chair
New Image Plastic Surgery Associates

Gretta Stone
Board Secretary-Treasurer
Director
Reservoir Communications Group

Shontelle Dodson, PharmD
Senior Vice President
Head, Medical Affairs Americas
Astellas Pharma Inc.

Dawn Halkuff, MBA
Chief Commercial Officer
TherapeuticsMD

—

Anne B. Cropp, PharmD
Chief Scientific Officer
Early Access Care LLC

Nieca Goldberg, MD
Medical Director
Joan H. Tisch Center for Women's
Health, NYU Langone Health

Linda G. Griffith, PhD
Professor of Biological Engineering
Massachusetts Institute of Technology

Jenelle S. Krishnamoorthy, PhD
Associate Vice President, Global Policy
Merck & Co. Inc.

David C. Page, MD
Director, Whitehead Institute
Massachusetts Institute of Technology

Judith K. Wolf, MD
Gynecologic Oncologist
Community Health

Alan T. Wright, MD
Chief Medical Officer
Roche Diagnostics Corporation

Michael Ybarra, MD
Vice President,
Medical Affairs and Strategic Alliances
PhRMA

—

Florence Haseltine, PhD
Founding Honorary Board Director
Executive Director of Health Research,
University of Texas at Arlington

June 10, 2019

Submitted electronically to: publiccomments@icer-review.org

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

Dear Dr. Pearson:

The Society for Women's Health Research (SWHR) appreciates the opportunity to provide input to the Institute for Clinical and Economic Review (ICER) on the 2020 update to its value assessment framework. SWHR, an education and advocacy thought leader, is dedicated to promoting research on biological differences in disease and improving women's health through science, policy, and education.

SWHR is committed to ensuring value frameworks are appropriately designed and used to inform decision-making to achieve optimal health outcomes for women as patients, caregivers, and health care decision-makers for themselves and their families.

- Women comprise more than half (51%) of the U.S. population.¹
- Women provide the majority of caregiving.
 - Nearly 70% of caregivers are female.²
 - Women assume multiple roles while caregiving: hands-on caregiver, case manager, companion, decision-maker, and advocate.
- Women make more than 80% of health care spending decisions.³

SWHR is pleased to offer these comments and suggestions on how ICER can improve the methods it uses to work with stakeholders and to assess the value of drugs and health care interventions.

1. Account for diversity in patient populations and subgroups (including sex and gender).

Sex and gender play critical roles in the risk, pathophysiology, presentation, diagnosis, treatment, and management of disease. As defined by the Institute of Medicine:

- Sex refers to the classification of living things according to reproductive organs and functions assigned by chromosomal complement.⁴
- Gender refers to the social, cultural, and environmental influences on the biological factors of women or men. Gender is rooted in biology and shaped by environment and experience.⁵

When women are underrepresented in clinical trials, outcomes from predominantly male cohorts have driven clinical guidelines that are not sex specific.⁶ The increased study of sex and gender differences is leading to important discoveries of how women and men differ in fundamental ways and how these differences affect disease risk, symptoms, diagnostic sensitivity and specificity, and response to therapy. Biological and physiological differences and hormonal fluctuations have been shown to play a role in the rate of drug absorption, distribution, metabolism, and elimination, resulting in different drug responses in women and men.⁷

ICER's value assessment framework should account for diversity in patients (including sex and gender) for a given disease state by analyzing data that represents relevant patient populations and subgroups.

2. Explore subpopulation value metrics.

ICER's framework takes a population-level perspective versus a shared decision-making tool approach for use by patients and their clinicians, and ICER acknowledges the limitations of representing patient diversity with a population-level focus:

*"Representing the diversity of patient outcomes and values in a population-level framework is difficult because there will always be an inherent tension between the average findings in clinical studies and the uniqueness of every patient."*⁸

Given these limitations, ICER should improve upon its methodologies to incorporate patient subgroup outcomes and preferences for treatment into its value framework. As discussed above, examining patient subgroups is imperative to understanding how patients may respond differently to therapy and health interventions based on factors such as sex and gender, age, genetic variation, stage of illness (e.g., severe vs. mild disease, advanced vs. early disease), and comorbidities (absence vs. presence).

Value frameworks such as ICER's should capture patient heterogeneity and have the analytic capability to report more than a single value-based price for an average patient. We urge ICER to explore opportunities for building subpopulation value metrics into its model, such as subpopulation cost-effectiveness ratios (e.g., male vs. female), which could present a way to account for treatment option optimization among patient populations more narrowly.

3. Ascertain whether clinical trial data are representative of the relevant patient population.

ICER's current value framework relies heavily on clinical trial data for its evaluations. Predominant reliance on clinical data can underrepresent certain patient populations and subgroups, such as women and people of racial and ethnic minority groups.

ICER should incorporate methods to evaluate whether the clinical trial data used in a given value assessment are representative of the relevant patient population and subgroups. SWHR encourages ICER to review publicly available data sources to inform this determination. For example, the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA) posts online [Drug Trial Snapshots](#) that show who participated in pivotal clinical trials used to approve a novel drug that is either a new molecular entity or original biologic product. The Snapshots stratify the clinical trial data by sex, race, age, and ethnicity groups, and also provide statements on observed differences in safety and efficacy by demographic subgroups at the time of approval. CDER has published a Snapshot for each novel drug approved within one month of the official FDA approval date since January 2015.

Drug Trial Snapshots for three FDA-approved drugs for migraine report that 85% or greater of the participants enrolled in FDA clinical trials to evaluate safety were women.⁹ This percentage is consistent with the population affected by the condition, which affects women differently than men,¹⁰ and shows that women were represented as a population subgroup in the clinical trial data.

4. Quantify factors that matter to patients and society and integrate them into ICER value assessments.

ICER's Patient Guide to Open Input for its 2020 value framework update states that "it is critically important that the patient perspective be fully captured in [its] work."¹¹ SWHR strongly agrees that any value assessment should aim to understand the diversity of the patient experience. Examples of burden of illness factors that are important to women include (but are not limited to):

- Survival
- Ability to work
 - Presenteeism
 - Absenteeism
 - Employment disability
- Quality of life
 - Physical and social well-being
 - Pain or discomfort
- Levels of disease burden and progression
- Comorbid conditions
- Caregiver burden¹²

- Permanent difficulty, stress, or negative experiences resulting from providing care¹³
 - Physical, emotional, and financial cost of the caregiving
- Limitations in treatment
 - None
 - Limited options

ICER's current approach deems factors like these as "additional benefits/contextual considerations" and does not formally incorporate them into its assessment results. By leaving them up to the discretion of the voting panel, their impact is not being systematically measured. To provide a comprehensive picture of a treatment's value, ICER's value assessments should quantitatively account for a broad array of factors that are important to patients and society, such as those listed above.

5. Use a broad range of high-quality, real-world evidence sources.

Patients have characteristics and treatment experiences that often differ from the controlled environment of clinical studies. Data on caregivers — the majority of whom are women — have not been routinely collected in clinical trials. That is why understanding how treatments work in real-world clinical settings — with input from patients and caregivers — is so important.

[Real-world evidence](#) is derived from data collected during routine health care practice (such as electronic health records, claims and billing activities, or product and disease registries) and is often collected *after* a new therapy is already on the market and being used by patients. As the availability of RWE grows, all value assessment organizations, including ICER, should seek to increase the use of a broad range of high-quality RWE sources in its reviews.

SWHR is pleased that ICER has stated its intent to explore ways to incorporate RWE into its work. While RWE will not be available for new drugs at launch, it may be available for marketed products and can be useful for therapeutic class reviews and updated reviews by providing critical information to assess whether outcomes are different by sex and gender.

As part of its 2020 framework update, ICER should outline its process and systematic approach for increased use of RWE in future topic reviews. ICER's approach should review recent and current RWE initiatives and seek to leverage existing resources, information, and best practices, instead of initiating de novo work in this area. Some examples include:

- In December 2018, FDA released a [detailed framework](#) outlining how the agency will evaluate RWE intended to support approval of a new indication for an approved drug or biologic, or to help support or satisfy drug post-approval study requirements. This framework will serve as a roadmap for the inclusion of real-world data (RWD) and RWE in regulatory decisions, including standards on how RWD is defined, collected, and analyzed. FDA will also provide guidance on RWE study methodologies and designs that

meet regulatory requirements in generating evidence of effectiveness, among other topics.

- On July 11 and 12, 2019, the Robert J. Margolis, MD, Center for Health Policy at Duke University will convene a public stakeholder workshop to examine considerations for using randomized designs to generate RWE. The public workshop is a part of ongoing efforts to explore the utility of RWE and inform FDA's strategic framework.
- In July 2017, National Health Council convened a daylong, multi-stakeholder roundtable to gather patient community views on RWE and related concerns as well as the communications, information, and tools needed by patients to understand, trust, and use RWE. A [published report](#) followed outlining 10 themes that emerged from the discussion.¹⁴

6. Leverage existing approaches for systematically capturing patient and caregiver input.

Generating high-quality patient data that addresses patient needs is of great interest and priority to diverse stakeholders throughout the U.S. health care system. Recent legislation — the 21st Century Cures Act and sixth authorization of the Prescription Drug User Fee Act (PDUFA VI) — gave FDA significant new directives to address patient needs as part of advancing medical innovation. [FDA's Patient Focused-Drug Development \(PFDD\) Program](#) is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation by:

- facilitating and advancing systematic approaches for collection and use of robust and meaningful patient and caregiver input to more consistently inform drug development and regulatory decision-making;
- encouraging identification and use of approaches and best practices to facilitate patient enrollment and minimize the burden of patient participation in clinical trials;
- enhancing understanding and appropriate use of methods to capture information on patient preferences and the potential acceptability of tradeoffs between treatment benefit and risk outcomes; and
- identifying information that is most important to patients related to treatment benefits, risks, and burden, and how to best communicate the information to support their decision-making.

SWHR encourages ICER to review patient experience data sources and methods outlined in FDA draft guidance (and public comments in response to them) to inform how this initiative and significant work to date could be leveraged and incorporated in ICER's value assessment framework.

In May, the National Alliance for Caregiving, in partnership with the LEAD Coalition, published [Paving the Path for Family-Centered Design: A National Report on Family Caregiver Roles in Medical Product Development](#). The report highlights where caregiver insights might be most useful at each stage of medical product research and development and presents recommendations

for leveraging the existing policy and emerging practices to tap the wisdom of caregivers about the conditions their care recipients experience and the health care outcomes that matter most. SWHR encourages ICER to draw upon “Paving the Path” report findings and recommendations to identify ways to better integrate caregivers and their perspectives into ICER’s value assessment framework.

7. Develop standards for using patient experience data in value frameworks.

SWHR strongly supports the development of consensus-driven standards for patient data collection, submission, and management. To be reliable and effective, such standards must be based on methodologically sound approaches that accommodate the distinct and varying perspectives of patients on the value of interventions, while simultaneously collecting patient experience data that is relevant, objective, accurate, and representative of the target patient population. Standards should be flexible, with the capacity to evolve over time. As stakeholders gain more experience with data collection, submission, and management, standards and processes may need to be revisited and revised.

SWHR encourages ICER to facilitate constructive dialogue with key stakeholders including industry, patient advocacy organizations, and federal agencies to allow for a transparent and organized process for developing standards for the collection, submission, and management of patient experience data used in value assessments.

8. Elaborate on ICER’s use of cost-effectiveness analysis (CEA) registry data in value assessments.

A January 15, 2019, press release issued by the Tufts Center for the Evaluation of Value and Risk in Health (CEVR) announced that ICER had begun using the [CEVR cost-effectiveness analysis \(CEA\) registry](#) — a comprehensive database of 7,287 cost-utility analyses on a wide variety of diseases and treatments published from 1976 to 2017 — to help evaluate drugs and other medical interventions.

ICER has provided limited details about how it is using the CEVR CEA registry in its topic reviews. SWHR could not find any mention of the CEVR CEA registry on ICER’s website. As part of its update to the 2020 value assessment framework ICER should discuss in a transparent manner how it is using the CEVR CEA registry in topic reviews.

9. Align timing of value assessments with availability of pertinent data.

ICER often conducts its reviews before complete data are available. In some instances, ICER has determined cost-effectiveness of a therapy ahead of its market introduction and public announcement of its price. For example, ICER conducted its assessment of cholesterol-lowering PCSK9 inhibitors before clinical trials were completed. In its draft evidence report on endometriosis, ICER repeatedly acknowledged important limitations both in the available evidence and in its own analysis, calling into question the timing of the value assessment and the validity of its conclusions. Missing or incomplete data lead to a flawed valuation. SWHR urges

ICER to trigger the timing of its topic reviews when pertinent data (clinical trial, accurate pricing, and real-world evidence) are available.

10. Extend stakeholder review times.

Value assessment organizations should provide ample opportunities for stakeholder engagement to ensure their input is both acknowledged and meaningfully incorporated into assessments. ICER should announce proposed assessment topics, processes, and timelines in advance to allow for participation by stakeholders, especially those with limited resources. ICER should also allocate sufficient time for stakeholders to review materials and submit comments in various stages throughout the assessment process. Assessments should be regularly updated to account for new innovation and other changes in the evidence base.

SWHR appreciates that ICER “adheres to tight timelines for each report in order to balance timing of expected drug approvals with decision-makers’ need for timely information to inform policy and practice.”¹⁵ While we understand that comment periods need “to be limited to ensure ICER staff to review comments and incorporate them into reports,”¹⁶ we urge ICER to further reflect on the numerous comments expressing concern with the timeline for public comment submissions. Three weeks is not sufficient time for stakeholders — particularly small, under-resourced ones — to respond. Extending the timeline even by a few weeks would be helpful for stakeholders to engage and provide meaningful review and feedback.

11. Foster greater transparency of value assessment, processes, methodologies, and results.

Explanation of value assessment criteria, methodologies, and assumptions should be understandable to patients and other stakeholders. Models and data should be publicly available to allow others to analyze the research and replicate results.

SWHR commends ICER for its commitment to a transparent public engagement process to ensure that all stakeholders have the opportunity to provide input to its reports and updates to its value assessment framework. We were pleased that ICER took steps last year to make draft executable economic models available to manufacturers during the assessment review process. While we agree with ICER that enabling the direct viewing of a model’s structure, estimates, key assumptions, and calculations may allow for valuable feedback during the public comment period that follows the release of an ICER draft evidence review, ICER’s current approach has limitations. Access to the models remains too restrictive. ICER should make models available to qualified researchers, not just for review but for customization and reproducibility, and it should relax confidentiality agreements to foster greater discussion among interested parties.

Thank you for considering the above input. We look forward to serving as a resource on this and other topics affecting women’s health. If you have questions or if we can provide further information to inform ICER’s update to its value assessment framework, please contact Sarah

Wells Kocsis, Vice President of Public Policy, at 202.496.5003 or swellskocsis@swhr.org.

Sincerely,



Amy Miller, PhD
President and Chief Executive Officer
Society for Women's Health Research

¹ Kaiser Family Foundation State Health Facts. Population Distribution by Gender. 2016 Timeframe.

<https://www.kff.org/other/state-indicator/distribution-by-gender/>. Accessed February 2018.

² Family Caregiver Alliance. Who Are Family Caregivers? <https://www.apa.org/pi/about/publications/caregivers/faq/statistics>. Accessed May 2019

³ Becker's Hospital Review. April 2015. <https://www.beckershospitalreview.com/hospital-management-administration/women-make-80-percent-of-healthcare-decisions.html>

⁴ Institute of Medicine. Exploring the biological contributions to human health: Does sex matter? Washington, DC. National Academies Press, 2001.

⁵ Ibid.

⁶ Ghare, M. Sex Disparities in Cardiovascular Device Evaluations. Strategies for Recruitment and Retention of Female Patients in Clinical Device Trials. Journal of Cardiovascular Interventions.

⁷ US Food and Drug Administration Drug Trial Snapshots. www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm

⁸ Institute for Clinical and Economic Review. Overview of the ICER value assessment framework and update for 2017-2019.

⁹ US Food and Drug Administration Drug Trial Snapshots. www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm

¹⁰ GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Lancet. 2017 Sep 16;390(10100):1211-1259.

¹¹ Institute for Clinical and Economic Review. 2020 Update to ICER's Value Assessment Framework: A Patient's Guide to Open Input. May 2019.

¹² Burden C, Quite NRS. A practical guide to caring for caregivers. Am Fam Physician. 2000;62:2613–2620. <https://www.ncbi.nlm.nih.gov/pubmed/11142468>. Accessed April 2019.

¹³ Simon BS, Budó MDL, Garcia RP, et al. Social support network to the caregiving family of an individual with a chronic disease: integrative review. Journal of Nursing UFPE on line [JNUOL/DOI: 10.5205/01012007] 2013;7:4243–4250. [Google Scholar]

¹⁴ Oehrlein, E et al. Patient-Community Perspectives on Real World Evidence: Enhancing Engagement, Understanding and Trust. The Patient. Patient-Centered Outcomes Research. January 2019. <https://doi.org/10.1007/s40271-019-00356-z>.

¹⁵ Institute for Clinical and Economic Review. Overview of the ICER value assessment framework and update for 2017-2019.

¹⁶ Ibid.



June 10, 2019

VIA ELECTRONIC DELIVERY

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

Re: Public Input for 2020 ICER Value Assessment Framework

Dear Dr. Pearson:

Spark Therapeutics (“Spark”) is pleased to submit comments regarding the Institute for Clinical and Economic Review’s (ICER) “2020 ICER Value Assessment Framework.” Given Spark’s areas of research and development, our comments address the ways ICER’s general value assessment framework can better represent the cost-effectiveness of innovative, one-time therapies. Although we appreciate ICER’s efforts thus far to adapt its general framework to acknowledge the complex issues surrounding informed decision-making relating to ultra-rare disease (URD) therapies,¹ we remain concerned about the ability of uniform cost-effectiveness analysis (CEA) frameworks to accurately and comprehensively value one-time life-changing therapeutic options generally. Under the existing uniform CEA framework, lack of specific distinctions recognizing such elements of value as scientific spillover/innovation, hope, lessening disease severity, productivity and equity of outcomes, for example, may result in suboptimal allocation of expenditure/investments in healthcare in the long-run, simply in the name of short-term savings.² We are aware ICER is working on creating a framework specific to evaluation of one-time curative therapies; in the meantime, our comments recommend improvements to the general ICER framework that has been used to evaluate one-time therapies to date.

¹ According to ICER’s value assessment framework for ultra-orphan diseases, ICER will consider using an adapted approach to value assessment for treatments that will be called a “potential major advance for a serious ultra-rare condition” if the following criteria apply:

- An eligible patient population for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

(see ICER, “Modifications to the ICER value assessment framework for treatments for ultra-rare diseases – Final Version,” November 2017. Available at: <https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf>).

² Lakdawalla, Darius N. et al. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report. Value in Health, Volume 21, Issue 2, 131 – 139.

The focus of our comments is to encourage ICER to consider improved methods to better illustrate the value of one-time therapies, particularly for URDs, within its framework.

In the comments below, we outline six issues for ICER to consider when evaluating its value-assessment framework for both standard and therapies to treat URDs:

- I. Presentation of both discounted and undiscounted incremental Quality Adjusted Life Years (QALYs), costs, and ICERs;
- II. Appropriate consideration of the long-term and/or lifetime benefits of one-time treatments;
- III. Explicit inclusion of indirect costs in ICER's assessment of long-term value for money;
- IV. Consideration of the entire supply chain of pharmaceuticals in the determination of value-based prices;
- V. The scientific/evidential basis for value-based price benchmarks for URD therapies; and
- VI. The use of standard benchmarks in the assessment of long-term value for money of URD therapies.

About Spark Therapeutics

Spark Therapeutics is a fully integrated, commercial company committed to discovering, developing, and delivering gene therapies. Our goal is to challenge the inevitability of genetic diseases by bringing treatments to patients for blindness, hemophilia, lysosomal storage disorders, and neurodegenerative diseases. As you know, we brought the first Food and Drug Administration (FDA)-approved gene therapy for an inherited genetic disease to market in the US, voretigene neparvovec-rzyl (LUXTURNA®) for *RPE65*-mediated inherited retinal disorder (IRD) and worked productively with ICER throughout its review of LUXTURNA. Since LUXTURNA was launched in early 2018, more than 100 vials have been used to treat patients with *RPE65* biallelic mutations, illustrating Spark's ability not only to achieve regulatory approval for the first gene therapy in the US, but to successfully commercialize the first gene therapy in the US as well. It is these experiences, and successes, upon which we base many of our recommendations outlined below.

Spark's Comments

Spark concurs with ICER's recognition of the need for further stakeholder input and engagement on its current value-assessment framework. Although Spark's product pipeline is focused on the development of one-time gene therapies for mostly rare and ultra-rare diseases, we provide recommendations for both ICER's general framework as well as its URD framework below.

General Framework Comments

- I. The framework should present both discounted and undiscounted QALYs, costs, and ICERs to address the bias against one-time therapies implicit in a discounted analysis*

Since the costs associated with one-time gene therapies are predominantly up-front but benefits are accrued over time, discounting practices used in economic analyses bias against one-time

therapies, in similar fashion to the bias against preventative therapies recognized in the literature.³ Thus, it is important that ICER provide cost-effectiveness results for both discounted and undiscounted analyses in its reports. In fact, ICER's own reference case for economic evaluations indicates both discounted and undiscounted outcomes should be reported; however, this does not appear to be done consistently in practice in ICER's final evidence reports.⁴ Not only does reporting undiscounted values provide more transparency in the calculation of the cost-effectiveness measures, it allows readers to understand the difference discounting assumptions may have on the final assessment of "value for money". As such, we believe it should be standard practice to provide both discounted and undiscounted results (costs, QALYs, and ICERs) in ICER's final evidence reports and ICER should consider the undiscounted results in their assessment of long-term value for money when discounted and undiscounted ICERs vary appreciably from one another.

II. The framework should appropriately consider long-term and/or lifetime benefits of treatments as appropriate

One aspect of gene therapies is that they are expected to have durable or long-lasting effects from a one-time administration. While Spark acknowledges that there can be uncertainty surrounding the durability of effect for a gene therapy at the time of regulatory approval, frameworks that unnecessarily curb treatment effect duration and do not provide for sensitivity analyses, and/or effectively communicate the implications of such analyses, will not adequately reflect the range of potential benefits these one-time treatments provide to patients. This is particularly true of gene therapies developed for URDs, where a paucity of data for small patient populations makes determinations around long-term benefits more difficult to ascertain. Importantly, it should be recognized that a lack of evidence beyond a certain length of follow-up is not evidence of a lack of efficacy beyond that point.

Spark suggests that ICER's framework include specific guidelines surrounding the range of durations to be tested and that the framework allow for testing a lifetime benefit when appropriate. These ranges should be part of any standard reporting that ICER releases for transformative therapies. Reporting results under a range of assumptions for the duration of effect acknowledges the inherent uncertainty pertaining to this key aspect of these therapies. To the extent that ICER would like to comment on the degree of uncertainty around different assumptions, such comments must not be speculative, and instead ground themselves in the available evidence (e.g., based on statistical extrapolation of clinical data).

It is also important to note that there are long-term or potentially lifetime benefits to one-time, transformative therapies that come from the reduced treatment burden associated with a one-time

³ Per Severens and Milne (2004): "On pragmatic grounds, since discounting discriminates against well-accepted, once-off preventive and other programs that are characterized by early investment and late health outcome, including screening and pediatric vaccination, some authors argue that future benefits of such programs should not be discounted. If this principle were accepted, it might be necessary to develop detailed guidelines for discounting the benefits of other types of well-accepted health-care programs such as lipid screening coupled with (ongoing) lipid lowering therapy, which are also designed largely for risk management."

Severens JL, Milne RJ. Discounting Health Outcomes in Economic Evaluation: The Ongoing Debate. *Value in Health*. 2004;7(4):397-401.

⁴ ICER, "ICER's Reference Case for Economic Evaluations: Principles and Rationale," July 16, 2018. Available at: https://icer-review.org/wp-content/uploads/2018/07/ICER_Reference_Case_July-2018.pdf

treatment. Even with similar efficacy to a chronic therapy, a one-time treatment can have additional benefits for patients due to a decreased administration burden and a reduction in potential adverse events from administration of chronic therapies, not to mention a reduction in the psychological effects that go along with long-term, chronic treatments.⁵ One-time therapies may also improve adherence to therapy—by removing the need to adhere to a treatment regimen—particularly in treatment of chronic conditions, enhancing the real-world effectiveness and by consequence patient outcomes.⁶ Thus, ICER should seek to appropriately acknowledge these distinguishing features of one-time, transformative therapies.

III. The framework should explicitly consider indirect costs in its assessment of long-term value for money of a therapy

Spark supports the inclusion of “other benefits and standards” and “contextual considerations” that ICER has included as part of its URD framework. Spark strongly agrees with the need for consideration of factors outside of the disease state that are additive to the overall value of a treatment. Both indirect and direct costs of diseases and disorders impede patients, their families and caregivers, health systems, education systems, and governments attempting to mitigate the infliction.

Although ICER includes the “societal perspective” in their final report for URD therapies and discusses the indirect costs and the burden of the disease borne by families at the Comparative Effectiveness Public Advisory Council (CEPAC) meetings, the societal perspective results are not usually included in press releases or summaries of the ICER final report. As a result, Spark believes ICER should not only include indirect and family-borne costs (e.g., caregiver burden in costs and health utility) in its base case analysis but present these results alongside any “payer perspective” results they determine in a clear and concise manner.

IV. The framework should consider the entire healthcare supply chain in the determination of a value-based price rather than focusing solely on list price

The price listed by a manufacturer for a therapy is rarely the price actually paid by payers for the therapy. For many therapies, the supply chain from manufacturer to patient is a complicated one, including multiple intermediaries such as wholesalers, pharmacy benefit managers (PBMs) and pharmacies.⁷ A manufacturer may provide incentives to these intermediaries to carry their product in the form of discounts or rebates off the list price. Although the contractual arrangements that define discounts and rebates are confidential, the literature indicates that the final price paid by the payer is often below the list price.⁸ As ICER has recently noted,

⁵ Turner J and Brian Kelly B. Emotional dimensions of chronic disease. *West J Med*. 2000 Feb; 172(2): 124–128. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1070773/>

⁶ Lakdawalla, Darius N. et al. “Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report.” *Value in Health*, Volume 21, Issue 2, 131 – 139.

⁷ United States Government Accountability Office. “DRUG INDUSTRY Profits, Research and Development Spending, and Merger and Acquisition Deals.” GAO-18-40 Report. November 2017. Available at: <https://www.gao.gov/assets/690/688472.pdf>.

⁸ Congressional Budget Office. “Prices for and Spending on Specialty Drugs in Medicare Part D and Medicaid.” Reported Sourced from Working Paper 2019-02. March 2019. Available at: https://www.cbo.gov/system/files/2019-03/54964-Specialty_Drugs.pdf; Mattingly, T. Joseph et al. “Estimating Drug Costs: How do Manufacturer Net Prices Compare with Other Common US Price References?” *PharmacoEconomics*. 2018; 36: 1093.

intermediary actors in the supply chain do not usually pass on the value of these rebates/discounts in full to the payer.⁹ Thus, the list price (i.e., the Wholesale Acquisition Cost (WAC) price), the price a drug is evaluated on in ICER's value-based assessment, does not represent the actual price most manufacturers charge or receive for a therapy.

Furthermore, for physician-administered drugs delivered in, for example, the hospital outpatient setting, the "buy and bill" method results in a price much higher than the WAC. Under this method, the provider (physician or hospital) buys the product either from the manufacturer or a specialty distributor and administers the product to the patient. Upon administration, the provider files a claim for the drug which typically includes a billable charge that is arbitrarily marked up 2.5 to 6 times the WAC. The health plan then contracts with the provider for reimbursement of the drug at 60% to 80% of the billable charge. For example, the actual cost to the health plan/employer for an \$2,000,000 drug would start at \$3,000,000 on the low end of the aforementioned range. These mark-ups have been cited publicly and can be verified with health plans.¹⁰

If ICER is truly looking to evaluate whether the price of a therapy coincides with a value-based price, they need to incorporate a price more reflective of what the manufacturer offers in the real-world and pay more scrutiny to other actors in the current system/supply chain beyond manufacturers that are responsible for higher prices to end-users including payers, employers, and even patients.

Ultra-rare Framework Comments

V. The framework should rely on appropriate value-based price benchmarks that reflect scientific, social, or policy justifications

Value-assessment frameworks, which may impact market access for therapies, should be developed in consideration of other policies around rare-disease therapy development. Drummond et al. (2007) note that "[i]t does not make much sense (in terms of efficiency) for the public system to fund or subsidize R&D on orphan drugs and later not reimburse the resulting innovations. This strategy will lead to a waste of R&D resources (if the products are finally not used) and discourage future investment on R&D on orphan drugs."¹¹ Application of a static cost-per-QALY range as the basis for calculating value-based price benchmarks implies that willingness to pay is consistent across health benefits of all types, while studies of societal preferences indicate otherwise. Preferences have been shown for giving priority to treatments for more severe and urgent conditions.¹² Some studies have also indicated a preference for assigning a higher priority to

⁹ Cole, Amanda et al. "Value, Access, and Incentives for Innovation: Policy Perspectives on Alternative Models for Pharmaceutical Rebates." ICER and OHE Research Whitepaper. March 2019.

¹⁰ Spark Therapeutics. "Spark Therapeutics Announces First-of-their-kind Programs to Improve Patient Access to LUXTURNTM (voretigene neparvovec-rzyl), a One-time Gene Therapy Treatment. Press Release. January 3, 2018. Available at: <http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-announces-first-their-kind-programs-improve>.

¹¹ Drummond MF, Towse AK. Orphan drugs policies: a suitable case for treatment. Eur J Health Econ. 2014;15:335-40.

¹² Linley WG, Hughes DA. Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain. Health Econ. 2013;22(8):948-64.

Nord E. Cost-value analysis in health care. New York: Cambridge Press; 1999.

Dolan P, Shaw R, Tsuchiya A, Williams A. QALY maximisation and people's preferences: a methodological review of the literature. Health Econ. 2005;14(2):197-208.

treatments for younger patients (although it has been difficult to quantify the magnitude of this preference),¹³ and for patients with rare diseases.¹⁴

While societal preferences for allocation of healthcare expenditures may seem difficult topics to account for in ICER's URD framework, many of the most prominent users of such frameworks have recently taken steps to do so. As examples, in both England and the Netherlands, the health-technology assessment bodies (NICE and Zorginstituut Nederland [ZiN]) have weighted QALY gains by adjusting cost-per-QALY threshold for magnitude of incremental QALY gains (generally reflective of the severity of the disease and the lack of alternative treatment/unmet need) and for disease severity, respectively.¹⁵ NICE's proposed approach to QALY weighting for URDs (as part of its "highly specialised technologies" process) involves use of an incremental cost-per-QALY threshold ranging from 5 to 10 times the standard level,¹⁶ depending on factors such as the severity of the disease and the lack of alternative treatment (unmet need.)¹⁷ Applying such adjustments to ICER's standard thresholds, for example, value-based-price benchmarks of \$100,000 to \$150,000, would suggest use of a range of \$500,000 to \$1,500,000 in the adapted framework for URDs.

ICER does not offer analysis or any explanation for why its value-based-price benchmarks and thresholds for rare-disease, innovative therapies are considerably lower than those used by NICE in England for highly specialised technologies (HSTs) that usually apply to ultra-orphan drugs. We urge ICER to reconsider the determination of its threshold ranges for ultra-orphan therapies.

VI. The framework should not rely on standard value-based benchmarks in the determination of an URD's long-term value for money

We are also concerned that although CEA results are shown for a number of thresholds up until \$500,000 in ICER's final value assessment reports for URD therapies, the value-based-price (VBP) benchmarks for URD therapies are determined using the same thresholds as for non-URD therapies (\$100,000 to \$150,000). As Spark experienced with ICER's review of LUXTURN, despite there being scenarios in the final report that suggested the therapy could be cost-effective

Brazier J, Ratcliffe J, Tsuchiya A, Salomon J. Measuring and valuing health benefits for economic evaluation. Second ed. Oxford: Oxford University Press; 2007. 287-96.

¹³ Tsuchiya A. The value of health at different ages. Discussion Paper No. 184. University of York Centre for Health Economics 2001. Tsuchiya A, Dolan P, Shaw R. Measuring people's preferences regarding ageism in health: some methodological issues and some fresh evidence. Soc Sci Med. 2003;57(4):687-96.

¹⁴ Drummond MF, Towse AK. Orphan drugs policies: a suitable case for treatment. Eur J Health Econ. 2014;15:335-40.

Linley WG, Hughes DA. Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain. Health Econ. 2013;22(8):948-64.

¹⁵ Raftery J. NICE's proposed new QALY modifier for appraising highly specialised technologies The BMJ Opinion 2017 [updated 18 April 2017]. Available from: <http://blogs.bmj.com/bmj/2017/04/18/nices-proposed-new-qaly-modifier-for-appraising-highly-specialised-technologies/>.

National Institute for Health and Care Excellence. NICE gets go-ahead to fast-track more drug approvals NICE 2017 [updated 15 March 2017]. Available from: <https://www.nice.org.uk/news/article/nice-gets-go-ahead-to-fast-track-more-drug-approvals>.

Zwaap J, Knies S, van der Meijden C, Staal P, van der Heiden L. Cost-effectiveness in practice. Zorginstituut Nederland; 2015 26 June 2015.

¹⁶ In the UK, NICE uses an incremental cost-per-QALY threshold range of £20,000 - £30,000 in standard technology appraisal. It has proposed that HSTs with cost/QALY ≤ £100,000 (5 times the lower bound of the standard range) would receive coverage, and that for those with cost/QALY > £100,000, the threshold would be £10,000 x the incremental QALYs up to a maximum threshold of £300,000 (10 times the upper bound of the standard range).

¹⁷ These factors are common drivers of large incremental QALY gains.

at higher thresholds¹⁸, the takeaway by many in the media and by payers was that the therapy was not cost-effective because of ICER's focus on the lower thresholds (i.e., that VBP benchmarks were only reported for willingness-to-pay (WTP) thresholds of \$100K and \$150K per QALY).¹⁹

By reporting VBP benchmarks for the same thresholds as for standard therapies, ICER reports may be understood to imply that considerations around thresholds should not materially differ between standard and URD, innovative therapies. Thus, along with the contextual considerations, Spark encourages ICER to revisit the thresholds for URDs used in reporting VBP benchmarks, and to report more clearly why different thresholds might be relevant to innovative therapies for URDs. For example, the long-term implications of using the same WTP thresholds on the allocation of expenditure on/ investment in healthcare should be considered, as well as other dimensions of value (and thus potentially WTP) that are excluded from current frameworks (see Lakdawalla et al. (2018)²⁰).

Conclusion

Spark appreciates the opportunity to comment on the current "2020 ICER Value Assessment Framework." As noted above, we support the reporting of undiscounted results and lifetime scenarios to address the biases that come with applying a general framework to one-time, transformative therapies. Beyond that, it is important that all the potential value of a treatment, including reductions to indirect costs and improved indirect utility, are a part of the assessment for any therapy. We further ask that ICER consider the broader inefficiencies related to the drug distribution system, rather than focusing their efforts solely on the manufacturer's list price. We also encourage ICER to exercise caution when assigning value thresholds for URDs and update its framework to be more balanced.

We hope the above comments are helpful to ICER in updating the methods it uses for its evidence reports; we look forward to reviewing the draft framework and providing additional feedback upon its release. Please do not hesitate to contact me at sarah.pitluck@sparktx.com or 202-431-6706 with any questions.

Sincerely,



Sarah Pitluck
Head, Global Pricing & Reimbursement

¹⁸ "Age 3, Modified Societal Perspective" at thresholds of \$150K/QALY and higher, and "Age 3, US Health Care Perspective" and "Age 15, Modified Societal Perspective" at the \$500K/QALY threshold and higher.

¹⁹ Berkrot, Bill, "Spark's price for Luxturna blindness gene therapy too high: ICER," Reuters, January 12, 2018. Available at: <https://www.reuters.com/article/us-spark-icer/sparks-price-for-luxturna-blindness-gene-therapy-too-high-icer-idUSKBN1F1298>.

²⁰ Lakdawalla DN, Doshi JA, Garrison LP Jr, et al. Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report. Value Health. 2018 Feb;21(2):131-139.

June 9, 2019

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

Dear Dr. Pearson:

We are writing in regards to the request for public comments on the Institute for Clinical and Economic Review (ICER) 2020 Value Assessment Framework.

First, we extend our appreciation to your team for the sustained commitment to advancing and improving the methods of value assessment for health technologies in the United States. The ICER organization has developed substantially in size, scope, and methods. We would like to submit the following comments for your team to consider in the 2020 iteration of the ICER value framework:

1. Reference Case Considerations
2. Family Spillover Effects

Reference Case Considerations

The ICER framework document specifies a “population-level” perspective to evaluate evidence to support those making guidelines, coverage determinations, and other population-focused decisions. We understand this approach and support that stated goal, and we strongly urge ICER to consider a standard reporting of items frequently captured in the societal perspective in addition to the typical health sector / direct medical cost approach that is frequently reported as the primary analysis. The Second Panel on Cost Effectiveness in Health and Medicine recognized that the societal perspective (originally recommended as the preferred reference case) was rarely conducted and modified their recommendations such that economic models should report both perspectives and produce an impact inventory to aid in decision making.^{1,2} Currently, the ICER framework suggests that productivity effects will be included for most analyses. We strongly support this and also encourage that results from this perspective be reported in the final results tables when performed.

We understand that there may often be a paucity of evidence supporting the burden of indirect cost categories, but that doesn’t limit a modeler from attempting to estimate these costs in order to provide greater context for the ICER committees who make the final vote. An important step is to determine the relevance of these costs, as well as others such as caregiver time (discussed further below), for individual analyses. This suggests a role for patient engagement earlier in the modeling process. Eliciting patient experience information helps quantify the importance of various societal perspective impacts as well as clarify other base-case model inputs.

Family Spillover Effects

In addition to the missed costs described above when focusing on direct medical costs, how the ICER framework formally accounts for potential spillover benefits in the denominator could help represent the true benefits to the population at-large, given the stated population perspective. While the societal perspective

analysis attempts to capture more costs important to caregivers (co-payments, childcare, and opportunity costs due to caregiver productivity losses), the utility gains do not account for potentially quality of life gains attributed to a caregiver or immediate family member – potentially underestimated the true societal value.^{3,4}

Again, to address whether family spillover effects are relevant impacts for a particular model, early patient engagement would help clarify this need.

We hope that these comments are helpful as you finalize your Value Assessment Framework. We thank you for your willingness to consider public comments for future iterations of your framework.

Sincerely,



Julia Slejko, PhD
Assistant Professor
Pharmaceutical Health Services Research



Joey Mattingly, PhD
Assistant Professor
Pharmacy Practice & Science

References

1. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA J Am Med Assoc. 1996;276(15):1253-1258.
2. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses. JAMA. 2016;316(10):1093-1103. doi:10.1001/jama.2016.12195.
3. Brouwer WBF. The Inclusion of Spillover Effects in Economic Evaluations: Not an Optional Extra. Pharmacoeconomics. 2018;37(4):451-456. doi:10.1007/s40273-018-0730-6.
4. Lin P-J, D'Cruz B, Leech AA, et al. Family and Caregiver Spillover Effects in Cost-Utility Analyses of Alzheimer's Disease Interventions. Pharmacoeconomics. 2019;37(4):1-12. doi:10.1007/s40273-019-00788-3.



Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210
www.vrtx.com

June 10, 2019

***BY ELECTRONIC DELIVERY* (publiccomments@icer-review.org)**

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

Re: Input for 2020 Value Assessment Framework

Dr. Pearson:

Vertex Pharmaceuticals, Inc. (Vertex) appreciates the opportunity to submit comments to the Institute for Clinical and Economic Review (*ICER*) regarding an update to its value assessment framework (VAF). While we communicated last May about your review of our cystic fibrosis (CF) medicines as part of the 2018 evidence report, this letter reiterates Vertex's views on areas for improvement in the way that *ICER* assesses the value of rare disease medicines.

Vertex is a global biotechnology company headquartered in Boston, Massachusetts that invests in scientific innovation to create transformative medicines for people with serious and life-threatening diseases. Vertex discovered and developed the first and only medicines to treat the underlying cause of CF, a rare and medically complex disease affecting about 30,000 individuals in the United States. Today, Vertex has three FDA-approved products for the treatment of CF in certain patients: SYMDEKO® (tezacaftor/ivacaftor and ivacaftor), ORKAMBI® (lumacaftor/ivacaftor), and KALYDECO® (ivacaftor). On May 30, 2019, we announced that we selected a triple combination regimen, elexacaftor in combination with tezacaftor and ivacaftor, to submit for global regulatory approvals with a submission of a new drug application (NDA) in the U.S. planned for the third quarter of 2019. We believe this triple combination regimen has the potential to treat up to 90 percent of patients living with CF.

Vertex believes that there are three specific areas of *ICER*'s VAF that could be altered to provide a more accurate estimate of a drug's value: (1) increasing the threshold to calculate

value-based price benchmarks (VBPBs) for rare disease therapies; (2) acknowledging the limitations of the VAF for life-extending therapies for chronic, rare conditions and providing a range of possible VBPBs, including an estimate of undiscounted life-years; and (3) broadening the definition of “value” to include other elements more concretely in the evaluation process. We discuss each of these areas in more detail below.

* * *

I. ICER’s current VBPBs are not appropriate for rare disease therapies.

In 1983, recognizing the lack of available therapies for individuals suffering from rare diseases, Congress passed the Orphan Drug Act (ODA),¹ which provided several incentives for manufacturers to invest in the development of drugs used to treat rare diseases. While the ODA has been undeniably successful in spurring innovation,² of the approximately 7,000 rare diseases that affect 25 to 30 million people in the United States, still only five percent have treatments.³

In modifying its VAF for “ultra-rare” diseases, *ICER* acknowledged that a willingness-to-pay (WTP) threshold of up to \$500,000 per quality-adjusted life year (QALY) should be used. At the same time, *ICER* declined to adjust its VBPB, keeping it at between \$100,000 to \$150,000 per QALY.⁴ While the \$100,000 to \$150,000 per QALY threshold may be appropriate for common diseases where large patient populations drive returns on investment that allow for lower unit prices, such a threshold is inappropriate for rare disease therapies. Indeed, Congress acknowledged as much in passing the ODA, noting that “because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug...”⁵ The ODA was intended to improve the financial incentives of investing in rare diseases, and has been broadly successful in achieving this goal. Beyond this, therapies that are truly innovative for diseases that have not seen advancement in decades are inherently less likely to achieve *ICER*’s cost-effectiveness thresholds due to the relatively inexpensive nature of the comparators, despite, in many cases, substantial impacts on morbidity and mortality. *ICER*’s current thresholds are thus unlikely to be met for rare disease therapies because they fail to account for this reality. In the case of Vertex, its therapies are the *first and only* medicines to treat the underlying cause of CF and have fundamentally changed both the short- and long-term course of the disease, but the current thresholds do not acknowledge this innovation.

In addition, *ICER*’s “ultra-rare” prevalence cutoff of 10,000 individuals is not well-supported and unfairly penalizes medicines that treat diseases with a prevalence only marginally above this threshold. Under *ICER*’s framework, for example, a drug used to treat a disease that

affects only slightly more than 10,000 individuals would be evaluated no differently than a drug used to treat a disease with a prevalence in excess of ten million. *ICER* justifies its position by stating that it “believe[s]” that difficulties in conducting clinical trials and recouping development costs are no longer applicable to drugs with patient populations of greater than 10,000 and asserts that “it is *ICER*’s experience” that conducting randomized controlled trials with adequate outcome measures can be conducted above that threshold.⁶ Such an assessment is not only at odds with the U.S. Congress, which defined a rare disease as one that is intended to treat fewer than 200,000 people in the U.S.,⁷ but also with the European Union (5 in 10,000) and Japan (less than 50,000).⁸ By using a prevalence cutoff of 10,000 individuals, *ICER* is ignoring the special recognition that society has granted to orphan therapies and is instead substituting its own opinion on how these medicines should be valued.

Recommendation: *ICER* should increase the willingness-to-pay threshold in calculating the VBPB for drugs with orphan indications, defining those to be more closely aligned with the well-established definition in the U.S., to include \$500,000 per QALY, consistent with the reporting in the cost-effectiveness (CE) tables.

II. *ICER*’s current VAF is biased against life-extending therapies for chronic, rare conditions.

While *ICER*’s VAF simulates many scenarios for inclusion in the Evidence Report, its current approach is to provide one incremental CE ratio to determine the VBPB. This method leads to a false sense of precision and minimizes the myriad of factors that can impose an undue influence on the resultant incremental CE ratio. This is of particular concern as many factors affecting the CE ratio are arbitrary modeling assumptions that are not tied to the clinical value of the product being evaluated. For life-long therapies used to treat rare, genetic conditions and for which the life-extending benefits are accrued far into the future, there are four key elements that inappropriately influence the incremental CE ratio: (1) the discount rate; (2) assumptions regarding pricing dynamics over time (i.e., generic entry); (3) multifactorial benefits not captured in the QALY; and (4) the costs of managing the disease during the period of extended life.

Discount Rate: By design, the concept of discounting values costs and benefits accrued today more highly than those accrued in the future. When this approach is applied to costs and health effects of medicines, chronic therapies that extend life are penalized, while interventions that treat conditions where patients die within a short time period are far less impacted. Medicines which can be taken from an early age with the aim of slowing disease progression and delivering extended survival benefits far into the future are particularly impacted by the discount rate. This high degree of sensitivity to the chosen discount rate in

evaluations of lifelong therapies has been recognized by health technology assessment agencies, most notably by the National Institute for Health and Care Excellence (NICE) in England, which recommends that lower discount rates should be considered for therapies where “treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years).”⁹ Indeed, recent literature suggests that costs and health effects should be discounted at different rates.¹⁰ A recent analysis evaluating the cost-effectiveness of Kalydeco found that switching from a traditional 3.0 percent discount rate applied to both costs and health outcomes to a differential discount rate of 3.0 percent for costs and 1.5 percent for health outcomes reduced the incremental CE ratio by over 50 percent, and that the undiscounted survival gain of 20.9 life-years was reduced to 4.1 life-years when 3 percent discounting was applied.¹¹ The disproportionate influence of the chosen discount rate in the *ICER* model highlights how traditional CE frameworks are inherently biased against lifelong therapies for chronic conditions, where the important benefits take years to materialize.

Pricing Dynamics: *ICER* methods do not allow for the inclusion of known pricing dynamics over time, whereby prices for small molecule treatments decrease substantially after loss of exclusivity (LOE), typically by 80-90 percent.^{12,13} While many therapies that *ICER* reviews are not used to treat life-long conditions from a very young age—and thus are not highly impacted by these pricing dynamics—therapies that treat patients for upwards of 30 years will almost certainly be subject to these well-documented price decreases. For example, in the same recent analysis of Kalydeco as discussed above, assuming a price reduction at the time of expected generic entry was shown to result in a 65 percent reduction in the incremental CE ratio.¹⁴ In declining to take this real-world pricing into account, *ICER* justifies its position by arguing that to do so “would add an additional layer of uncertainty and speculation to our analysis,” and that “[e]stimating such changes may be especially difficult in the US market.” At the same time, *ICER* acknowledges that “[g]eneric drugs are generally expected to have discounted pricing relative to branded competitors,” and even provides citations to several CE analyses in CF that take into account the loss of patent exclusivity.¹⁵ This assumption not only biases the analysis against life-saving therapy used in chronically ill patients requiring life-long treatment, it is internally inconsistent. By failing to take into account at least *some* level of price decrease upon patent expiration, *ICER* appears to be professing—with 100 percent certainty—that there will be *no* level of price decrease. Such a conclusion is contrary to the weight of the evidence.¹⁶

Multifactorial Benefits: For many genetic diseases that are present at birth, demonstrating gains in quality of life based on currently-used quality of life measurements is extremely challenging. Because patients adapt to their condition, they tend to score themselves highly in terms of their quality of life on the current “standard of care” treatments because they are used to living with their condition and have no other experience to compare it against. The

resulting “ceiling” effects makes it challenging to significantly improve these scores with the addition of new therapies and, as a result, direct quality of life gains from novel treatments are poorly captured in *ICER*’s current approaches to cost-effectiveness modeling. Additionally, the QALY collapses the multifactorial benefits of therapies into a single outcome measure that fails to capture the full benefits of these treatments. For example, in the *ICER* model, utility scores may be based on only one or two outcomes, thus omitting several other quality of life benefits that may not be mediated through the assessed outcomes. This approach may ignore documented benefits of therapies on other organ systems and general improvements in well-being and quality of life not related to the assessed outcomes. Solely basing quality of life improvements on what has been directly measured at the time of *ICER*’s evaluation ignores important elements of quality of life for novel therapies, particularly when some of these benefits may take years to be observed. Moreover, the impact on caregiver and societal quality of life is not adequately captured in the existing framework; although *ICER* does assess a “societal perspective” as a scenario under the “ultra-orphan” framework, this typically makes little difference to the resultant *ICER* due to the lack of available evidence at the time of the review. In the analysis of Kalydeco noted above, a treatment-specific utility increment was applied to capture the missing elements of quality of life for the patient and caregiver, which resulted in as much as a 25 percent reduction in the incremental CE ratio.¹⁷

Costs of Managing the Disease: *ICER* considers the total lifetime costs associated with a new medicine, including the disease management costs incurred during the period in which the treatment extends a patient’s life. While these costs can be small for medicines that do not extend life or only extend life for a short period of time, for medicines that lead to substantial increases in survival versus the comparator—and where the condition is chronic and the patients will continue to have the disease for the entire model horizon—these additional costs essentially penalize the medicines for extending the lives of patients. In essence, the longer a patient lives, the more expensive they are to the system, and the higher the cost per QALY. Such a formula devalues life-extending therapies, which is counterintuitive to how society values such medicines.

Recommendation: *ICER* should, at a minimum, acknowledge that its current approach penalizes life-extending therapies for chronic, rare conditions and provide a range of possible VBPs, to eliminate the false precision placed on providing a single VBP. Additionally, we recommend *ICER* implement the following adjustments to the base-case, particularly for life-extending therapies that treat chronic, rare, genetic, conditions and for which the important benefits take years to materialize:

1. Apply **differential discount rates** to costs and health effects, whereby health outcomes have a lower discount rate than costs.
2. **Include price reductions at the time of generic entry**, for products that are used over several decades and for which this well-documented phenomenon will almost

certainly occur. *ICER* can consider applying different assumptions to different types of medicines (e.g., small molecule vs. biologics) to reflect well established pricing dynamics. Moreover, although patent-life can change during the course of a products lifecycle, *ICER* can estimate both the time of patent expiry and the amount by which the price will drop with some reasonable amount of certainty based on the available data.

3. Allow for **broader definitions of quality of life** that fully capture the patient and caregiver experience, even if the evidence has not been systematically collected at the time of the *ICER* assessment. By failing to make a good-faith attempt to estimate these benefits based on analogue conditions or expert opinion from clinicians, patients and caregivers, as is commonly done for important model inputs, *ICER*'s current approach values these additional benefits at zero.
4. Include a scenario that **excludes disease management costs during the period of extended survival**; where these costs are substantial enough to drive the resultant *ICER*, this analysis should represent the base-case.

III. *ICER* should broaden its definition of “value” to include other elements more concretely in the evaluation process.

While *ICER* includes a section in its final report titled “Other Benefits and Contextual Considerations,” these aspects are not factored into the final VBPB unless there are firm values associated with them. For example, when evaluating CF therapies, *ICER* conceded that “CF represents a major and lifelong burden to patients and their caregivers,” that CF therapies “may improve both unadjusted and quality-adjusted life expectancy,” and that “CFTR modulators are the only available intervention that targets the basic pathophysiology of the disease.” Indeed, for patients and families, the ability to manage their condition and go to school or work makes a huge difference on both a personal and socio-economic level. Still, *ICER* largely ignored these benefits in calculating its VBPB, dismissing their value as “difficult to estimate” or “yet to be reliably quantified.”¹⁸ Given that *ICER* typically evaluates a medicine proximal to its U.S. approval date, there is little room for any evidence to exist outside of what can be measured in a clinical trial. *ICER* thus presents an impossible standard to meet by demanding quantifiable evidence of other benefits for inclusion into the CE model that are challenging to measure and/or take time to measure adequately, but no formal way to consider these important elements that would most certainly impact resultant incremental CE ratios without such quantifiable evidence. Requiring this high standard of evidence is not conservative and effectively values these other benefits at zero, even when there is ample qualitative evidence that their true value is substantial. This default assumption of zero value calls into question *ICER*'s seriousness about accurately estimating and incorporating these benefits.

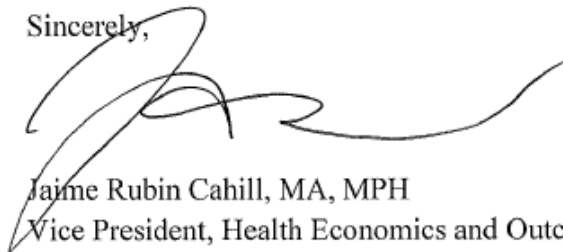
An additional important element of value is the projected impact on life-expectancy, specifically for novel, innovative medicines in rare disease. Given the impact of survival is often diluted by the application of utilities and the discount rate, especially for chronic conditions, documenting the *undiscounted* life-years as a projection of the impact of a therapy on survival is critical to the evaluation.

Recommendation: *ICER* should include other elements of value more concretely in their evaluation process and attempt to include them in the economic evaluation through reasonable scenario analyses. In addition, *ICER* should systematically include undiscounted life-years gained in the assessment to ensure the projected impact of novel therapies on patient survival is adequately considered.

* * *

As we have noted previously, we are concerned that *ICER*'s current process is not constructive from a patient access perspective and is ill-suited for complex, rare diseases such as CF. Our therapies offer major improvements in quality of life and/or length of life for many patients with CF,^{19,20} and we remain concerned that *ICER*'s VAF fails to adequately capture these benefits. Vertex has committed more than twenty years to the development of medicines that treat the underlying cause of CF and has brought to market three medicines that do exactly that, impacting thousands of lives in the process. We stand by the value of our medicines and the long-term benefits that they bring to people with CF. We sincerely hope that *ICER* takes the above recommendations into account in revising its VAF, and we welcome the opportunity to address any questions you may have about the information above.

Sincerely,



Jaime Rubin Cahill, MA, MPH
Vice President, Health Economics and Outcomes Research
Vertex Pharmaceuticals

¹ Orphan Drug Act. Public Law 97-414. January 4, 1983.

² National Organization for Rare Disorders. Trends in Orphan Drug Costs and Expenditures Do Not Support Revisions in the *Orphan Drug Act*: Background and History. 2017.

-
- ³ IQVIA Institute. Orphan Drugs in the United States: Growth Trends in Rare Disease Treatments. October 2018. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments.pdf?_=1558021310570.
- ⁴ ICER. Modifications to the ICER value assessment framework for treatments for ultra-rare diseases. November 2017. <https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf>.
- ⁵ Orphan Drug Act. Public Law 97-414. January 4, 1983.
- ⁶ ICER. Modifications to the ICER value assessment framework for treatments for ultra-rare diseases. November 2017. <https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf>.
- ⁷ 21 U.S.C. § 360bb(a)(2).
- ⁸ Richter T, Nestler-Parr S, Babela R, et al. Rare Disease Terminology and Definitions—A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. *Value in Health*. 2015; 18:906-14.
- ⁹ National Institute for Health and Clinical Excellence. Discounting of health benefits in special circumstances. April 9, 2018. <https://www.nice.org.uk/guidance/ta235/resources/osteosarcoma-mifamurtide-discounting-of-health-benefits-in-special-circumstances2>.
- ¹⁰ Paulden et al., 2017; Treasury Green Book in the UK). <https://www.ncbi.nlm.nih.gov/pubmed/27943173>.
- ¹¹ Lopez A, Rubin JL, Chandler C, Jena AB. Limitations of Cost-Effectiveness Methods When Analyzing Life-Extending Treatments for Rare, Chronic, Genetic Diseases: A Cystic Fibrosis Case Study. Presented at the 24th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research, New Orleans, LA, USA. May 18-22, 2019.
- ¹² Price Declines after Branded Medicines Lose Exclusivity in the U.S. IMS Institute for Healthcare Informatics, Parsippany, NJ. 2016. <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf>.
- ¹³ Dilokthornsakul P, Patidar M, Campbell JD. Forecasting the Long-Term Clinical and Economic Outcomes of Lumacaftor/Ivacaftor in Cystic Fibrosis Patients with Homozygous phe508del Mutation. *Value in Health*. 2017; 20(10):1329-1335.
- ¹⁴ Lopez A, Rubin JL, Chandler C, Jena AB. Limitations of Cost-Effectiveness Methods When Analyzing Life-Extending Treatments for Rare, Chronic, Genetic Diseases: A Cystic Fibrosis Case Study. Presented at the 24th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research, New Orleans, LA, USA. May 18-22, 2019.
- ¹⁵ ICER. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value. Final Evidence Report and Meeting Summary. June 7, 2018. https://icer-review.org/wp-content/uploads/2017/10/CF_Final_Evidence_Report_06082018.pdf.
- ¹⁶ Vondeling GT, Cao Q, Postma MJ, Rozenbaum MH. The Impact of Patent Expiry on Drug Prices: A Systematic Literature Review. *Applied Health Economics and Health Policy*. 2018; 16(5):653-660.
- ¹⁷ Lopez A, Rubin JL, Chandler C, Jena AB. Limitations of Cost-Effectiveness Methods When Analyzing Life-Extending Treatments for Rare, Chronic, Genetic Diseases: A Cystic Fibrosis Case Study. Presented at the 24th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research, New Orleans, LA, USA. May 18-22, 2019.
- ¹⁸ ICER. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value. Final Evidence Report and Meeting Summary. June 7, 2018. https://icer-review.org/wp-content/uploads/2017/10/CF_Final_Evidence_Report_06082018.pdf.
- ¹⁹ Volkova N, Bessonova L, Higgins M, et al. Real-World Outcomes in Patients With CF Treated With Ivacaftor: 2015 US and UK CF Registry Analyses. Poster presented at the 31st Annual North American Cystic Fibrosis Conference, Indianapolis, IN. *Pediatric Pulmonology*. (2017, November 2-4).
- ²⁰ Rubin JL, O’Callaghan L, Pelligra C et al. Modeling long-term health outcomes of patients with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor. *Ther Adv Respir Dis*. 2019.