



October 15, 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 on ICER’s proposed updates to the 2020 Value Assessment Framework. AAFA appreciates ICER’s willingness to engage with us and to better understand patients’ perspectives. We believe that thoughtful inclusion of patient experience data is essential to accurately reflect the true impact, and therefore “worth,” of new and evolving treatments. We offer the following comments on the current proposal:

Modified Social Perspective: In our initial comments in response to the Framework’s revisions, we urged ICER to include the modified societal perspective as part of the base analysis to more accurately reflect the patient perspective. Particularly but not solely in the context of food allergies, direct medical costs are just one component of the impact, and 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. We understand that the direct medical costs are of interest to many stakeholders (payers, in particular) and should be explicitly reported. However, we agree with the Second Panel on Cost Effectiveness that cost-effectiveness analyses should report two reference case analyses, one on the health care perspective and another the societal perspective, and produce an impact inventory to aid in decision-making.¹

We appreciate that ICER acknowledged and responded to this input from AAFA and other commenters. However, we are disappointed that ICER proposes to continue to use the health system perspective for its default base case. ICER notes only one category of exceptions:

- As per our methods adaptations for treatments of ultra-rare diseases, however, when the societal costs of care for any disease are large relative to the direct health care costs, the societal perspective will be included as a co-base case, presented directly alongside the health care sector perspective analysis.

¹ Sanders GD, Neumann PJ, Basu A, 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):1093–1103



We are concerned that this application of a societal perspective is both unduly narrow (limited only to ultra-rare diseases) and vague (societal costs “large relative to” healthcare costs). Using a societal perspective as one of two reference case analyses for *all* treatments where relevant societal data is available would provide a more robust and meaningful approach.

Customized Data Sets: As ICER noted in the draft proposal, multiple stakeholders argued for the inclusion of real-world evidence in ICER’s analyses. AAFA had been one of these stakeholders; we argued that, when available, real-world healthcare data, including claims and enrollment data sets, should be used to estimate the potential patient population and treatment effectiveness. We appreciate that ICER is committing to continuing to use high-quality real-world data where available, and that ICER proposes to identify opportunities to generate new real-world evidence when appropriate.

Sensitivity analyses: In our earlier comments, we encouraged ICER to run sensitivity analyses using multiple scenarios when appropriate. 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. We appreciate that ICER has proposed adding a section on “Controversies and Uncertainties” to the cost-effectiveness section of its reports in order to reflect alternative assumptions and models proposed by stakeholders, including but not limited to a manufacturer. However, we remain concerned that ICER’s approach will not sufficiently reflect the sensitivity of its models to multiple overlapping variables. In addition to the important step of identifying “Uncertainties” in its model, ICER should proactively run sensitivity analyses that reflect the impact of multiple variables. This information should be presented in a way that is clear and accessible to stakeholders.

Caregiver Burden: As AAFA has commented on multiple occasions, food allergies affect a whole family – as do nearly all health conditions. As we noted in the peanut allergy treatment letter, analyses should reflect not only potential diminished burden on caregivers, but should also reflect potential quality of life gains attributed to the caregiver, in order to reflect the true societal value of treatment. We encouraged ICER to fully reflect caregiver burden and potential benefits of interventions for caregivers in future analyses.

In the current proposal, ICER acknowledges such concerns, but argues that data on caregiver quality of life is limited and has key areas of uncertainty, including which family members to consider in such an analysis, and whether caregivers adjust to their burdens over time. Given the importance of caregivers and the enormous value of their quality of life along with the whole family’s quality of life, AAFA respectfully requests that ICER take a stronger stance on caregiver quality of life research, perhaps developing collaborations – as ICER proposes to do with regard to real-world-evidence overall – to define research needs and to generate knowledge in this area. In the meantime, we strongly support ICER’s proposal to use caregiver utility impact data when available.

Conclusion

ICER has an opportunity to expand its inclusion of the patient perspective and to lower both economic and quality of life costs for patients and their families. To do so, in addition to building relationships with patient groups, ICER should incorporate the patient perspective as part of their base-case economic analyses; use appropriate real-world data sets for their analyses to reflect the actual patient community;



Asthma and Allergy
Foundation of America

meaningfully present alternative assumptions and sensitivity analyses; and work to incorporate and grow the data on caregiver impact and quality of life.

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

October 18, 2019

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RE 2020 Value Assessment Framework: Proposed Changes

Dear Dr. Pearson,

Thank you for soliciting feedback on the “2020 Value Assessment Framework: Proposed Changes.” We are inspired by the Institute for Clinical and Economic Review (ICER)’s initiative to explore expanded uses of real-world evidence (RWE) in policy decision-making, and we at Aetion, Inc. share a common goal of using RWE in policy decision-making.¹

Our comments center on how transparent, auditable, and reproducible RWE — generated using principled database epidemiology — can enhance our understanding of product effectiveness and value, and help drive the critical transition to value-based care.² We encourage ICER and their stakeholders to:

1. Commit to principled database epidemiology;
2. Explore expanded uses of RWE for policy decision-making; and
3. Use a validated, rapid-cycle analytics platform.

1. Commit to principled database epidemiology

ICER’s role in standard setting, combined with their recently announced intention to augment their analyses by generating RWE, creates a unique opportunity to lead by example — specifically, to commit to generating RWE using principled database epidemiology. Multiple groups, including ICER, have detailed the challenges associated with developing and evaluating

¹ We define RWE in line with the FDA and ICER: “...the clinical evidence about the usage and potential benefits of risk of a medical product derived from analysis of RWD” (FDA. Framework for FDA’s Real-World Evidence Program, page 6, December 2018; ICER. Real World Evidence for Coverage Decisions: Opportunity and Challenges, page 9, March 2018).

² Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics.” JCE 2005; 58(4): 323-337. doi: 10.1016/j.jclinepi.2004.10.012.

RWE and have offered some suggestions on how to address them.^{3,4,5} However, there is a lack of universally accepted methodological and transparency standards, therefore we believe ICER must communicate their principles for ensuring transparency and principled RWE generation.^{3,5} At Aetion, we believe there are core principles when working with RWD and RWE and **we recommend ICER consider these principles when determining its framework for generating RWE.**

A summary of Aetion's principles is listed below. A detailed rationale for each principle can be found [here](#).⁶

Principles for using RWE to determine value

At Aetion, we believe that four principles increase confidence in RWE for policy decision-making. We call these principles the MVET framework:

1. **Meaningful evidence** that provides sufficient information and context to support interpretation, conclusions, and decisions;
2. **Valid evidence** that meets scientific and technical quality standards to allow causal interpretations;
3. **Expedited evidence** that provides incremental evidence while facilitating more timely decision-making; and,
4. **Transparent evidence** that is auditable, reproducible, robust, and ultimately trusted by decision-makers.^{7,8}

It is essential that these principles of RWE generation are applied to fit-for-purpose data in policy decision-making. We agree with ICER's assessment that various RWD sources, including electronic medical records and insurance claims, can be meaningful starting points for RWE generation. Principled database methodology, when applied to fit-for-purpose RWD, can mitigate confounding (bias) in the estimate of the treatment effect. We are committed to fostering use of RWE in policy decision-making, and we at Aetion believe these principles can guide the 2020 Value Assessment Framework.

³ Hampson, G., et al. Real World Evidence for Coverage Decisions: Opportunities and Challenges. March 2018. <https://icer-review.org/material/rwe-white-paper/>

⁴ Berger, M, et al. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Task Force on Real-World Evidence in Health Care Decision Making. Value in Health 2017; (20) 1003-1008.

⁵ HTAi Global Policy Forum. Real-World Evidence in the Context of Health Technology Assessment Process - from Theory to Action. December 2018. https://htai.org/wp-content/uploads/2018/11/Policy_Brief_GPF_2019_051118_final_line-numbers.pdf

⁶ <https://www.regulations.gov/contentStreamer?documentId=FDA-2018-N-4000-0014&attachmentNumber=1&contentType=pdf>

⁷ Schneeweiss S, et al. Real World Data in Adaptive Biomedical Innovation: A Framework for Generating Evidence Fit for Decision-Making. CPT 2016;100(6):633-646. Retrieved at <https://doi.org/10.1002/cpt.512>

⁸ Schneeweiss S, Glynn RJ. Real-World Data Analytics Fit for Regulatory Decision-Making. Am J Law Med. 2018;44(2-3):197-217. doi: 10.1177/0098858818789429

To define the methodological principles for generating decision-ready evidence for ICER, we encourage ICER to partner in demonstration project with its stakeholders. In the context of regulatory approvals, Aetion is collaborating with the U.S. Food and Drug Administration (FDA) to inform the inclusion of RWE in their decision-making frameworks through the [RCT DUPLICATE](#) project, in which researchers are using RWE to reproduce the results of 30 completed randomized controlled trials (RCTs) and to predict the results of seven ongoing RCTs. The FDA, Aetion, Brigham and Women’s Hospital, and Harvard Medical School are critically involved in developing a shared learning process to determine when an RWE study is or is not fit for FDA’s regulatory decision-making. The process of replicating an RCT with RWE (using principled epidemiology methods) and producing substantially similar results can validate the RWE analytic approach and inform stakeholders of the appropriateness of RWE methodology in specific situations (as well as when use of RWE is unlikely to be appropriate). We believe similar demonstration projects centered around ICER’s assessment process will be valuable in both validating RWE analytics and informing ICER’s methodology and transparency framework for generating RWE.

Once ICER has determined the framework for RWE generation that is fit for ICER assessments, complete with learnings from demonstration projects and best practices from experts in the field, **Aetion recommends that ICER publish their process and guiding principles for generating RWE.**

We appreciate that ICER is committed to “seeking and using existing RWE in its reviews” (line 385), and we are encouraged by their continued formal request for “stakeholders who are engaging in RWE generation to submit this for consideration” (line 391). This continued assessment of RWE’s fitness for use in regulatory and HTA decisions can reveal cases where RWE is better suited than an RCT may be to answer — or at least shed further light on — a study question. We agree that in many situations RCTs remain the gold standard for evidence of efficacy and are viewed as superior to RWE in evidence hierarchies.^{9,10,11} However, there are situations in which — for feasibility and ethical reasons — RWE generated using principled database epidemiology is better suited to answer the question at hand. For example, when the question is one of effectiveness in current clinical practice, principled RWE analysis may better answer the question than RCT data. RWE can capture patient cohorts not traditionally represented by RCTs e.g., women of childbearing age, patients 65 and older, and those with multiple comorbidities; and RWE can capture current clinical practice patterns and comparator product performance that are

⁹ Makady, A. Using Real-World Data in Health Technology Assessment (HTA) Practice: A Comparative Study of Five HTA Agencies. *Pharmacoeconomics* 2018;36:359-58.

¹⁰ Griffiths, E. The Role of Noncomparative Evidence in Health Technology Assessment Decisions. *Value Health* 2017; (20)1247-51.

¹¹ Malone, D.C., Real-World Evidence: Useful in the Real World of US Payer Decision Making? How? When? And What Studies? *Value Health* 2018;(21)326-33.

not always included in controlled clinical trial study design. **Rather than abide by evidence hierarchies, we recommend that ICER align their approach to evaluating the bias and study quality of published RWE to their principles of RWE generation, also taking into account best practice recommendations for RWE generation from ISPOR, ISPE, and others.**

2. Explore expanded uses of RWE for policy decision-making

Several decades of advancing scientifically rigorous methods, combined with increased access to RWD, creates an opportunity to expand the use of RWE for HTA decision-making.³ While newer methodologies developed over the last two decades have mitigated the biases present in non-randomized research, there is limited use of RWE in HTA agency decision-making. The research suggests two key reasons for this: the evidence hierarchies which place observational research as second tier and the lack of familiarity payers have in RWE methodology.^{8,12}

We are encouraged that ICER is committed to overcoming these challenges. At Aetion, we believe a commitment to integrating RWE into ICER assessments will enhance our greater understanding of therapies' effectiveness, value, and safety. However, in addition to formalizing the methodology and framework used to generate RWE, **we recommend that ICER explore and publish more specifics on how and when RWE will be used in the assessment process.** This transparency will help policymakers and manufacturers interpret and prepare, respectively, for ICERs assessments, and will add to the growing field of research on utilizing RWE for decision-making.

The "2020 Value Assessment Framework: Proposed Changes" document does not include substantial detail of how ICER would like to use RWE in their clinical effectiveness assessments. The document lists "comparative clinical effectiveness" (line 410), "long-term safety or durability" (line 412) and "potential other benefits" (line 413) as areas of emphasis, but we believe this list could be more specific on when and how RWE will be leveraged. We would welcome the opportunity to work with ICER to develop this list.

In addition, ICER states that they "will implement a formal process...to reassess whether new evidence has emerged that should be included in an update to the report one year after the release" (line 238). Given that this may be an ideal timeframe to utilize or further utilize RWE, we wonder if the document might detail whether and how RWE will be utilized in these reassessments. After a year of market access, the collection of available RWD will have grown (e.g., through claims and/or electronic health records data), and there is potential to support generation of RWE for comparative effectiveness and economic modeling enhancements. This has been highlighted as one of the benefits to RWE within the HTA process and we believe that ICER's reassessments would benefit from leveraging RWE to explore the evolution of clinical practice patterns and drug

¹² Malone, D.C., Real-World Evidence: Useful in the Real World of US Payer Decision Making? How? When? And What Studies? Value Health 2018;(21)326-33.

effectiveness results that could alter judgements on net-health benefit and value-based price.³ The ICER reassessments also represent an opportunity to further define a process of incorporating RWE in reassessments and move toward HTA management and disinvestment of non-effective therapies.

Again, **we encourage ICER to participate in wider demonstration projects that can identify cases where generating RWE will be beneficial to the ICER assessment and reassessment process, including projects that assess the impact of time since market approval on the RWE generation process and RWE's reliability and applicability to ICER's decision-making.**

3. Use a validated, rapid-cycle analytics platform.

Validated analytic platforms are an important mechanism to ensure the reliability, transparency, and reproducibility of RWE by ensuring good study quality and governance.^{6,7} Evidence of this includes the decision by key global regulators to employ such platforms for high stakes decision-making related to drug safety and efficacy.¹³ Such platforms support conducting rapid, transparent analysis, and provide a mechanism for fast sensitivity testing, thus reducing time to insights without sacrificing quality.^{14,15,16} **We recommend that ICER consider using a validated analytic platform to generate RWE.** Platforms allow for *principled study conduct*, *good study quality*, and *appropriate study governance*. We take each of the three in turn.

With respect to *principled study conduct*, an RWE analytic platform is a software product that is connected with one or multiple RWD sources and enables:

- The organization of raw data;
- The definition, implementation and documentation of measurements;
- The identification of relevant patient cohorts;
- The implementation of appropriate longitudinal study designs;
- The conduct and documentation of statistical analyses including appropriate risk-adjustment;

¹³ FDA partnered with Brigham and Women's Hospital and Aetion, leveraging the Aetion Evidence Platform for its DUPLICATE project on drug effectiveness ([PR Newswire, 5/8/18](#)); EMA licenses Aetion to support drug safety and pharmacovigilance.

¹⁴ Zhou, X. et al. Replication of Risk Characterization in a Cohort with Women with Advanced ER+/HER2- Breast Cancer Using a New Analytic Tool. Presented at the 35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Aug 2019.

¹⁵ Patorno E, Schneeweiss S, Gopalakrishnan C, Martin D, Franklin JM. Using Real-World Data to Predict Findings of an Ongoing Phase IV Cardiovascular Outcome Trial - Cardiovascular Safety of Linagliptin vs. Glimepiride. Diabetes Care. 2019 Jun 25. pii: dc190069. doi: 10.2337/dc19-0069. [Epub ahead of print]

¹⁶ Kim S, Solomon D, Rogers J, et al. Cardiovascular Safety of Tocilizumab Versus Tumor Necrosis Factor Inhibitors in Patients With Rheumatoid Arthritis: A Multi-Database Cohort Study. Arthritis Rheumatol. 2017 June;69(6):1154-1164.

- The reporting of results;
- The performance of sensitivity analyses and statistical diagnostics;
- The documentation of all study details in a complete and readable form while protecting patient privacy and controlling user access
- This documentation enables automatic creation and maintenance of audit trails, which is critical to support discussions among those who generate analysis and other internal or external stakeholders
- The ability to collaborate with colleagues on study implementation and share elements of study design (e.g., cohorts, measures, outcome definitions) across projects to promote efficiency and continuity.

Platforms ensure *good study quality* through:

- **Understandability:** Platforms allow for the specification of the study in terms that are easily understandable by decision-makers based on recommendations by, for example, ISPE and ISPOR,¹⁷ rather than through programming code, which is only understandable by statistical programmers.
- **End-to-end validation:** Platforms can be validated end-to-end, with the platform validation ensuring the accuracy of study implementations created on the platform. While line programming applications allow for great flexibility, validation of code requires diligent spot checking for each study, often by double programming. In addition to being time consuming, this routinely uncovers differences between programmers that need to be reconciled.
- **Validation against RCTs to show that RWE studies are “fit for purpose”:** Ongoing scientific validation against RCTs and other RWE studies will (re-)confirm that the platform can validly implement evidence given “fit-for- purpose” RWD.
- **Principled RWE study practice:** Platforms can ensure principled RWE study practice by guiding users to follow recognized paradigms in implementing comparative studies and limiting users to scientifically-valid analytic workflows. For example, a comparative effectiveness research (CER) workflow should be aligned with the “target trial” principle which aligns RWD- driven CER studies with the design of a hypothetical RCT that would have been used to assess the same causal question.¹⁸
- **Use of sensitivity analyses:** The scale achieved through platforms encourages relevant sensitivity analyses. Sensitivity analyses explore meaningful variations in design choices and definitions of key variables, as well as quantitative bias modeling, to inform

¹⁷ Wang SV, et al. Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0. Value Health 2017 (8)1009-22.

¹⁸ Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016 Apr 15;183(8):758-64. doi: 10.1093/aje/kwv254

decision-makers' ultimate confidence in study findings.¹⁹ Sensitivity analyses and replications are powerful tools to distinguish between spurious findings and causal associations, a critical distinction even when studies are pre-registered.

Platforms ensure *appropriate study governance*, through:

- **Transparent study implementation plan:** The RWE study implementation plan is always prepared and logged before the analysis is run.
- **Verifiable achievement of stated study intentions:** Platforms enable verification of the study implementation against the study protocol by other investigators, not only those able to read a particular programmer's code.
- **Audit capability:** Audit logs allow traceability and verification of what was done in the analysis, when, and by whom.
- **Long-term data capture and storage:** Long-term storage and capture of all study elements (cohorts, measurements, etc.) in the platform ensure long-term access to study materials and certain reproducibility.
- **Transparent data transformation:** Version histories and other provenance information for all study elements show changes (and rationale for changes) over time.

In addition to offering transparency and guiding principled database epidemiology, validated analytic platforms can improve efficiency and time to insights. ICER reviews are conducted on a tight schedule, e.g., eight weeks for standard review, 17 weeks for a class review, in order to meet decision-makers' needs. RWE generation will naturally add to the complexity of the assessments, so it is essential that generating RWE is feasible and efficient within the assessment timeline. Validated analytic platforms are more efficient than manual programming; a recent poster at the 35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE) found that a validated analytic platform (Aetion Evidence Platform[®]) reduced the time to generate cohorts and safety analysis from eight weeks to four weeks in a study of women with advanced ER+/HER2- breast cancer.²⁰ This gain in efficiency did not sacrifice quality as the results were “verified against traditional SAS programming and results were near identical.”¹⁸

At Aetion, we have a strong commitment to generating high quality, transparent, and validated RWE for decision-making and we are pleased with ICER's commitment to maximizing the use of RWE in its assessment process. We appreciate the opportunity to comment on the “2020 Value Assessment Framework: Proposed Changes.” Transparent and validated RWE— generated using

¹⁹ Gagne et al. for the FDA Sentinel Initiative. Analytical Methods to Assess Robustness of Drug Safety Monitoring Results. 2015.

²⁰ Zhou, X. et al. Replication of Risk Characterization in a Cohort with Women with Advanced ER+/HER2- Breast Cancer Using a New Analytic Tool. Presented at the 35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Aug 2019.

principled database epidemiology—can facilitate ICER’s goal of “fair pricing, fair access, and future innovation”.

Aetion looks forward to collaboration with the ICER to help facilitate the successful implementation and use of RWE in ICER’s assessment process. Please contact Carolyn Magill at carolyn.magill@aetion.com with any questions regarding these comments or other issues related to RWE policy and development.

Sincerely,

DocuSigned by:
Carolyn Magill
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Chief Executive Officer, Aetion

DocuSigned by:
Jeremy Rassen
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Jeremy Rassen, ScD.
President and Chief Science Officer, Aetion

October 18, 2019

Dr. Steven D. Pearson
President
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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) 2020 Value Assessment Framework proposed changes. 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.

Real World Evidence (RWE)

Robust collection of RWE is essential to truly measuring the efficacy and value of treatments, and we appreciate ICER's recognition of its importance. As we have stated in previous letters, clinical trial data is insufficient to capture the full scope of how treatments will work in patients. Both the opportunity and the challenge with incorporating RWE lie in the myriad ways in which RWE is currently collected, from registries to patient surveys and payer claims data.

We urge ICER to work closely with agencies like the Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS), private payers, providers, and patients to collect a robust set of data and work to standardize this data. The Arthritis Foundation collects Patient Reported Outcomes data using the PROMIS 29 and HCEQ measure sets. The PROMIS 29 open source framework, developed with funding from NIH and housed at healthmeasures.net, can be broadly applied to any patient population and could contribute towards standardizing collection of RWE.

We encourage ICER to bring disease-specific approaches to its assessments. Our selection of the indicated measures is the result of Nominal Group Technique and mixed methods approaches engaging more than 100 patients. Our experience in this program revealed challenges with other common PRO measures in this specific population. While ICER is likely not capable of developing these approaches in each disease state, the work required is vital and requires organization. ICER should commit to compensating participating organizations for patient engagement activities. The roles required by ICER also require resources and take patients and partnering organizations away from other mission related activities.

Cross-Reference with German Evidence Ratings

While an international approach is laudable, we raise concerns over the ability to extrapolate value across cultures. While guidance for evidence grading may be somewhat objective, the heart of the discussion is “benefit”. We express concern that the comment, “We propose to provide our own judgment of ‘added benefit’ within the German categories to complement ICER’s own methods” misses an opportunity to acknowledge the role of patients in defining benefit within the context of their local culture.

Quantifying Additional Dimensions of Value

We encourage ICER to not delay quantifying additional dimensions of value on the rationale. While we remain silent on the merits of the ISPOR recommendations, the issue of narrowly defined value is central to the challenges in ICER’s framework. We strongly encourage ICER to publicly document exploratory analyses of additional dimensions of value in future assessments.

Long Term Cost Effectiveness

We continue to be concerned about the reliance on Quality-Adjusted Life Years (QALY) in determining long-term value of treatments. ICER states that it will continue to use the \$100,000-\$150,000 per QALY as the standard for its value-based price benchmark for all assessments. If applied by payers, this threshold could easily disqualify all biologic medications for rheumatoid arthritis (RA) from being covered, per the 2017 ICER review of RA drugs. This is unacceptable and we urge ICER to work with the patient community and other stakeholders to develop a more appropriate, patient-centered approach to setting benchmarks.

We appreciate that ICER recognizes the near-universal concerns among the patient community on using QALYs. However, where ICER concludes that the QALY is the gold standard and will therefore continue to use it, we would argue that the QALY is an inappropriate standard. ICER should take the lead in the development of a new gold standard in close coordination with stakeholders.

Alternative Models

As ICER explores alternative models, it is essential to reference data from FDA activities like the Patient Focused Drug Development (PFDD) and Voice of the Patient (VOP) programs. For instance, willingness-to-pay and opportunity costs from the patient perspective are well documented in the two externally-led PFDD meetings the Arthritis Foundation has hosted.

What the quantitative and qualitative patient data show is that a one-size-fits-all methodological approach is not appropriate and will not adequately capture patient needs. We remain concerned that there is not sufficient variance between disease states, nor distinction made between therapeutic modalities, chronic versus acute disease, or patient preferences.

Payment Models

We appreciate the discussion of payment models and ICER's willingness to consider the impact of models like outcomes-based contracts on cost-effectiveness of treatments. Outcomes-based contracts and other value-based insurance models are being increasingly developed and implemented, and we agree this is an important area to consider in future assessments.

Potential Other Benefits and Contextual Considerations

We are pleased that ICER has taken steps to increase its emphasis of contextual considerations in recent years. Individual patient experiences do not often align with economic models, and there are many factors that influence patient treatment regimens and adherence, from overly burdensome utilization management requirements, to prohibitive out-of-pocket costs, caregiver burden, and inability to physically administer certain treatments, among others.

We have collected a significant amount of data to support the importance of contextual considerations among people with arthritis. For example, as we highlighted in our comments to ICER earlier this year, observations from our Live Yes! Arthritis Network strongly reinforce the notion that many or most RA patients:

- Cycle over several medications over the course of their disease;
- Change medications early in their disease treatment;
- Must overcome significant systemic barriers in order to receive doctor-prescribed medications; and
- 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.

Stakeholder Engagement

We are pleased that ICER will be adding stakeholder engagement components to its value framework, including discussion of how patient input is utilized in review and what suggestions are not adopted. This was a specific recommendation we submitted during the previous comment period and we thank you for its inclusion. Transparency of this nature will help instill confidence and understanding around ICER's decision making, which will in turn strengthen the ability of the patient community to engage with ICER.

We also appreciate the longer timeline for large class reviews and urge ICER to consider ways to ensure adequate timeframes for patient feedback for all reviews. As you know, few patient groups have the resources to adequately weigh in on reviews in the current timeframe, yet they have unique and valuable insights that are critical to ensuring an accurate review.

Report Updates

We are pleased that ICER is considering formalizing a process to receive updates on treatments post-market launch. How treatments are being utilized is an important component to inform the overall review. For example, ICER notes one factor to be considered is clinical practice patterns.

There are scenarios in which lower cost drugs come to market yet providers can't prescribe them because they are not on a patient's formulary; or a patient can't access them because they are on a restrictive tier. Collecting data on the impact of these and other barriers, in addition to positive treatment impacts, is essential to developing a more complete picture of comparative effectiveness in practice.

We have a few additional suggestions that are not in ICER's proposed changes but that we hope will be incorporated in the final report.

1. **Creation of a patient advisory committee.** As previously noted, the patient community is a critical stakeholder in providing patient perspectives to ICER reviews. The goals of this committee should include: advising ICER on the appropriate times and methods for engaging patients and patient groups; evaluating and helping develop standards for collection of RWE and for conducting patient surveys; providing guidance to patient groups whose disease areas are impacted by a review; and advising on the best ways to collect data on patient impacts of ICER reviews.
2. **Coordination with other value framework developers.** We strongly recommend that ICER consult with other value framework developers such as Avalere and FasterCure's Patient-Perspective Value Framework (PPVF) and the Innovation and Value Initiative (IVI). For example, 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. The latest recommendations can be found [online](#) and we encourage ICER to integrate these types of patient preferences and tools into the value framework.¹
3. **Collection and evaluation of ICER review impact.** As the number of ICER reviews grows, payers will increasingly use these reviews, whether to inform their Pharmacy and Therapeutics (P&T) Committee processes, or to adopt the recommendations. How these reviews are used in practice matters greatly, and we believe ICER has an obligation to ensure reviews are not being used to undermine patient care or lead to treatment barriers and worse health outcomes. ICER should formalize a process to evaluate the uptake and impact of its reviews once published.

The Arthritis Foundation appreciates the opportunity to comment on ICER's proposed changes. Thank you for your consideration of these suggestions, and please contact Anna Hyde at ahyde@arthritis.org with any questions.

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>



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RE: 2020 Value Assessment Framework Proposed Changes

Dear Dr. Pearson:

Aimed Alliance is a 501(c)(3) non-profit health policy organization that seeks to protect and enhance the rights of health care consumers and providers. Aimed Alliance respectfully submits the following comment in response to the “2020 Value Assessment Framework Proposed Changes” (“Proposed Changes”) published by the Institute of Clinical and Economic Review (ICER) on August 21, 2019.

I. ICER Should Revise Its Value Assessment Framework to Provide an Adequate Mechanism for the Inclusion of Real-World Evidence

Real-world evidence is emerging as an important consideration in drug development, regulatory approval decisions, and coverage decisions. The uses of real-world evidence include measuring adherence, establishing effectiveness among subpopulations, and establishing clinical and cost effectiveness within a health plan’s specific population.¹ ICER explains that it will assess the validity of real-world evidence and how such evidence should be incorporated into an assessment. ICER also intends to generate new real-world evidence for incorporation into its reviews.

Aimed Alliance is concerned that the Proposed Changes do not provide an adequate mechanism for the inclusion of real-world evidence into ICER’s cost-effectiveness review. ICER’s value assessments often occur before or shortly after the U.S. Food and Drug Administration (FDA) approves a therapy. As such, there is simply not adequate real-world evidence available for meaningful inclusion in a cost effectiveness assessment. Moreover, if a therapy is prematurely deemed not cost-effective, the likelihood of third-party payers covering the treatment without imposing significant benefit utilization management policies increases, creating barriers to access for patients who need innovative and life-saving therapies. Without market uptake, real-world evidence and its inclusion in subsequent cost effectiveness evaluations will be limited. As such, in addition to reaffirming its commitment to real-world evidence, we recommend that ICER refrain from making a determination about the cost effectiveness of new therapies until mature real-world evidence emerges in order to ensure its inclusion in ICER’s value assessments.

¹ <https://www.futuremedicine.com/doi/full/10.2217/cer-2018-0066>

II. ICER Should Incorporate Data Related to Indirect Costs to Patients into Its Value Assessment Framework

We thank ICER for seeking to work with the patient community as a partner through its Proposed Changes. The creation of a new “Patient Perspectives” chapter is a valuable addition to ICER’s evidence reports. The first-hand experience of living with a condition provides important cost-effectiveness data. Patient-reported outcomes, for example, are increasingly gaining importance in clinical research as a means of measuring changes to quality of life.²

However, the Proposed Change still does not incorporate meaningful data regarding the direct and indirect costs of therapies to patients into its calculations of value-based benchmark prices and potential budget impact. Such data provides valuable information about patient-based considerations for innovative therapies, such as measuring adherence to complex treatment regimens and indirect costs to caregivers. The exclusion of such information would certainly impact an accurate assessment of the value of innovative treatments and should be included. Aimed Alliance requests that ICER revise its framework to include such data.

III. ICER Should Consistently Include Patients and Medical Specialists in its Evidence Appraisal Council Membership

Patient advocates are included in ICER’s public meetings and have an opportunity to comment to provide input on cost-effectiveness evidence. Yet, they are notably absent from ICER’s voting evidence appraisal councils. Patients and caregivers provide a unique perspective about the value of new therapies about how living with a condition affects their quality of life. Though they are the only people who can provide this first-hand knowledge, their current role in ICER’s Value Assessment Framework is minimal.

Moreover, while specialists in the therapeutic area that is under analysis are included in the Value Assessment Framework and are often available to ICER’s voting councils at public meetings, they are not consistently included as members of ICER’s voting evidence appraisal councils. Medical specialists are uniquely positioned to provide insight into the intricacies of treating specific medical conditions and may better understand the challenges that their patients face regarding treatment access and adherence.

As such, Aimed Alliance recommends that ICER alter its council membership to establish minimum requirements for the inclusion of representatives from the patient community and medical specialists in the therapeutic area under review on its voting evidence appraisal councils. This will better ensure that specialists, patients, caregivers, and patient advocates are consistently included on its voting council memberships to provide meaningful patient engagement in its cost-effectiveness assessments.

² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227331/>

IV. ICER Should Provide Greater Transparency About the Evidence Evaluated Through the Value Assessment Framework

Aimed Alliance requests that ICER provide more transparency regarding the evidence being evaluated through its Value Assessment Framework, including information on study limitations, assumptions made, endpoints chosen, and model design used in its assessments. In particular, ICER has not provided any transparency on how it determines value-based benchmark prices and its potential budget impact analysis. ICER has not made its methodologies for clinical or economic evaluations transparent in such a way that outside researchers could test and validate its approaches. As such, we recommend that ICER make such information available.

V. ICER Should Not Rely on QALY to Evaluate the Value of a Treatment

Aimed Alliance reiterates its longstanding recommendation against relying on quality adjusted life year (QALY) measures to evaluate any treatment. The use of QALY measures to evaluate the value of a treatment raises significant ethical concerns. QALY measures put a price tag on the value of human life that merely reflects the individual's diagnosis and deems those with chronic, debilitating, and rare conditions as being worth less than those with common conditions. They treat individuals' lives and health as a commodity and ignore patients' and practitioners' individualized concept of the value of treatment.

QALYs are often used to justify coverage limitations and utilization management policies, such as prior authorization and step therapy programs, that prevent individuals from obtaining treatments that are most appropriate for their individualized needs. Prior authorization requires providers or insured individuals to obtain approval from the insurer or its pharmacy benefit manager before the plan will cover the cost of a prescribed health care product or service. Step therapy requires insured individuals to try and fail on alternative treatments, sometimes with adverse effects, before the payer will cover the prescribed treatment. Such policies can be unethical and inconsistent with standards of care, interfere with the patient-doctor relationship, and result in significant delays to prescribed treatments. For these reasons, we recommend against using QALYs.

Thank you for providing us with the opportunity to comment on the Proposed Changes. Please contact us at policy@aimedalliance.org or (202) 559-0380 if you would like to discuss any of the recommendations herein.

Sincerely,

A handwritten signature in black ink, reading "John Wylam". The signature is fluid and cursive, with the first name "John" and last name "Wylam" clearly distinguishable.

John Wylam
Staff Attorney

October 18, 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., is a biopharmaceutical company that develops and commercializes ribonucleic acid interference (RNAi) therapeutics. We believe in delivering transformative medicines for serious, high-unmet-need diseases and good value to patients, providers, payers, and society. We actively engage in conversations about value by working alongside payers and through commitments set forth in our Patient Access Philosophy.

Alnylam appreciates ICER's inclusion of a wide range of stakeholders in the process of updating its *2020 Value Assessment Framework*, and thanks ICER for consideration of our comments in response to its call for feedback on the framework. However, Alnylam believes additional consideration of the evidence is warranted for some aspects of the framework that ICER proposes to leave unchanged, and for other proposed updates that may unintentionally reduce the clarity or effectiveness of the framework. These elements of the proposed framework can have the unintended consequence of hindering access to life-changing treatments for patients, even when societal preferences would clearly support access.

With regard to the proposed *2020 Value Assessment Framework*, we believe ICER should give further consideration to addressing the following issues:

- 1. The ICER evidence rating matrix continues to have important limitations in terms of its precision and its ability to inform nuanced assessment of the clinical value of therapies under evaluation. Moreover, ICER's proposed modifications to the evidence rating matrix will further contribute to a lack of clarity about the value of new therapies.**

2. ICER's CEA models continue to insufficiently account for unique considerations relating to rare diseases and their treatments. Applying CEA to establish value-based price benchmarks for such treatments will thus lead to inappropriate characterization of value. Instead, we recommend that ICER evaluate rare disease therapies according to their affordability, which is the true driver of health system sustainability for these therapies. For other health technologies, CEA may be more appropriate, but should take into account elements of value beyond those specified in ICER's base-case framework.
3. ICER may treat therapies not categorized as "single or short-term transformative therapies" (SSTs) – particularly rare disease therapies not categorized as SSTs – differently from SSTs, without any true justification for doing so. Of note, ICER appears to be considering certain special allowances to account for evidentiary challenges in the case of SSTs, but not in the case of other rare disease therapies, which are known to face similar evidentiary challenges.
4. ICER's plan to seek collaboration opportunities for RWE generation is vague, does not explain the stakeholder engagement process, and does not specifically explain how RWE would be used.

1. The ICER evidence rating matrix continues to have important limitations in terms of its precision and its ability to inform nuanced assessment of the clinical value of therapies under evaluation. Moreover, ICER's proposed modifications to the evidence rating matrix will further contribute to a lack of clarity about the value of new therapies.

The additional ratings and cross-referencing to the German HTA methodology provide less clarity and complicate interpretation, without addressing the fundamental limitations of the matrix.

As noted in our initial response to ICER's call for feedback, the ICER evidence rating matrix – and in particular the letter-grade summary rating – is highly subjective, creating a false sense of precision and discouraging more nuanced assessment of evidence and unmet need by healthcare decision-makers. In addition, the evidence rating matrix does not consider the cost of increasing evidence quality by lengthening and expanding trials, which can harm patients in need of treatment.¹ This harm can be significant, and must be taken into account to reflect the reality that stakeholders inhabit when they make critical health decisions.

The proposed refinements to the evidence rating matrix – namely the addition of a new C++ rating category and the cross-referencing of ratings to German HTA ratings – do not address these fundamental limitations and create further confusion. For instance, although ICER describes situations where a C+ and C++ rating are appropriate, the differences between levels of certainty and benefit used to distinguish the C+ category from the C++ category are not explained, such that the ratings will be subjectively distinguished. As noted in the user guide, "a small difference in a quantitative score may be considered clinically significant in multiple directions, or not significant at all," and "[dis]agreements about the assessment of each domain and of the overall level of certainty are certainly likely, even among reviewers in the same group."² Adding new rating categories will do little to address the critical flaws of a rating process that is

already acknowledged to be coarse and subjective, and will thus not be valuable for providing additional useful information about interventions being evaluated.

Cross-walking evidence rating matrix grades to German HTA added benefit ratings also creates more complexity and less clarity on the results of the review. In particular, ICER states that they will “provide [their] own judgement of ‘added benefit’...rather than rate the evidence in the same manner as would be done in Germany.”³ The German ratings were designed to be used with the specific methodology developed by The Independent Institute for Quality and Efficiency in Health Care (IQWiG).⁴ Therefore, attempting to map ICER evidence rating matrix grades to German added benefit ratings without implementing IQWiG’s methodology is internally inconsistent and devoid of any true meaning. The result is to create further confusion and uncertainty in assessing the value of healthcare interventions.

Recommendations

- ICER should 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 consideration of evidence and unmet need by healthcare decision-makers.
- If ICER does opt to retain its current rating system, we do not believe that cross-walking to the IQWiG rating system is appropriate, as doing so – for consistency and interpretability – would require adopting the same IQWiG methodology designed to generate these ratings.

2. ICER’s CEA models continue to insufficiently account for unique considerations relating to rare diseases and their treatments. Applying CEA to establish value-based price benchmarks for such treatments will thus lead to inappropriate characterization of value. Instead, we recommend that ICER evaluate rare disease therapies according to their affordability, which is the true driver of health system sustainability for these therapies. For other health technologies, CEA may be more appropriate, but should take into account elements of value beyond those specified in ICER’s base-case framework.

CEA remains inappropriate as a price-setting tool for orphan therapies.

We reiterate our previously stated position that CEA is not an appropriate price-setting tool for rare disease treatments, due to (i) high uncertainty over willingness-to-pay thresholds in rare disease, (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) potential unintended consequences regarding incentives to develop new therapies for rare diseases. Instead, we recommend that ICER evaluate rare disease therapies using ICER’s affordability criteria and country-specific budgets, as affordability is what truly affects health system sustainability for rare diseases. Providing a realistic and credible analysis of a treatment’s budget impact would be of greater utility for payers and society than a highly uncertain CEA result.

In this regard, ICER can better help stakeholders understand the financial impact of a treatment by providing budget estimates that account for real-world usage patterns. In the past, ICER's uptake assumptions have been highly unrealistic, leading to overestimation of budget impact. A previous study found that ICER's estimates of uptake are 7 to 54 times higher than real-world uptake estimates.⁵

Even for non-orphan therapies, contextual considerations and additional dimensions of value must be incorporated into CEA to provide a fair assessment of value.

Rare diseases notwithstanding, even in other therapeutic areas where CEA may be more readily applicable, the ICER framework has important limitations in that it does not adequately capture meaningful contextual considerations and additional dimensions of value.

If valid, meaningful contextual considerations are not incorporated into pricing recommendations, they reduce stakeholders' ability to take these recommendations seriously. While we commend ICER for updating its report format to include the new "controversies and uncertainties" section and expand and clarify contextual considerations, failing to actually incorporate these aspects into the CEA means that the main assessment conducted by ICER is unrealistic and has limited value.

Of these contextual considerations, caregiver burden, in particular, is amenable to inclusion in CEA. It can be evaluated similarly to patients' QoL, and data on caregiver burden is often available.^{6,7} It is true that certain areas of uncertainty may arise, such as which family members to include in estimating caregiver burden. Nonetheless, there are several easily measurable components of this burden that have a direct economic impact and can be readily added to cost-effectiveness models, such as lost wages and foregone education and career opportunities. Including these elements would represent a lower bound for capturing the impact of caregiver burden. In addition, caregiver burden is experienced across demographic categories, and thus (in contrast to work productivity) does not raise issues with respect to age-based discrimination.

Recommendations

- We again urge ICER to publish results of CEA as a supplemental analysis for rare disease therapies, but not use CEA to inform price recommendations. Instead, ICER should evaluate rare disease therapy prices using ICER's affordability criteria and country-specific budgets.
- In assessing affordability, ICER should rely on historical real-world data from comparable disease areas to estimate more reasonable uptake figures for therapies under evaluation, as the method currently used by ICER continues to overestimate uptake.
- ICER should conduct further research on society's willingness to pay for rare diseases, as well as frameworks that appropriately capture the unique considerations influencing the true value of rare disease treatments. ICER's default model framework and base case should explicitly incorporate these considerations, which have major real-world impact and can often be valued empirically.
- In general, if evidence is available, ICER should incorporate novel components of value into any cost-effectiveness model in order to better reflect the reality of patients' lives.

The value of health technologies in addressing caregiver burden, in particular, can be readily evaluated.

3. ICER may treat therapies not categorized as “single or short-term transformative therapies” (SSTs) – particularly rare disease therapies not categorized as SSTs – differently from SSTs, without any true justification for doing so. Of note, ICER appears to be considering certain special allowances to account for evidentiary challenges in the case of SSTs, but not in the case of other rare disease therapies, which are known to face similar evidentiary challenges.

In its technical brief on valuing SSTs,⁸ ICER highlights a number of evidentiary challenges and associated areas of uncertainty that commonly affect SSTs – issues such as limited understanding of the natural history of the diseases targeted by SSTs, as well as small populations and serious, progressive symptoms that can limit the feasibility of randomized controlled trials and instead necessitate single-arm trials. Accordingly, ICER proposes a number of potential modifications to its general value framework to account for these evidentiary challenges for SSTs – for example, reporting of results for base-case, conservative, and optimistic modeling scenarios.

In the same briefing document, ICER acknowledges that such evidentiary challenges are not specific to SSTs but also apply more broadly to “many treatments for serious, and often rare, conditions”. Despite this, the proposed update to the *ICER 2020 Value Framework* does not express an intention to extend to all rare disease therapies all of the same special framework modifications that may be adopted for SSTs to deal with evidentiary challenges and related uncertainties.

In this regard, there is an apparently unjustified inconsistency between a potential SST value framework and the value framework used for other rare disease therapies. Other arbitrary inconsistencies exist as well. Notably, in our initial response to ICER, we recommended that ICER adapt its CEA framework to more accurately account for pharmaceutical pricing dynamics (including generic entry). ICER has declined to adopt this recommendation, with the rationale that attempting to model price changes would add further uncertainty to the CEA process.³ Despite this concern, ICER is incorporating the concept of health system savings due to dynamic pricing / loss of exclusivity into its proposed shared savings paradigm for evaluations of SSTs.

It is not internally consistent to include this concept in the evaluations of some technologies, but not others. Including the concept of dynamic pricing for certain evaluations also contradicts ICER’s claim that historical price data cannot be used to model the future. Dynamic pricing has in fact been widely studied and applied in the literature.^{9,10} Rates of generic entry and trends in prices are available throughout the literature, providing an excellent body of research on which to base estimates.^{9,11,12,13} Governments and organizations, such as the OECD, use rigorous methods to account for dynamic pricing in order to understand health expenditures and make budgeting projections.¹⁰ While estimates of the future are inherently imperfect, incorporating dynamic pricing is less incorrect than assuming prices are static forever and ignoring patent expiration.

Recommendations

- In the ICER value framework, any allowances granted to SSTs to account for evidentiary challenges and associated uncertainties should be extended to all rare disease therapies – not limited to SSTs – that are affected by similar challenges.
- The ICER model framework should also account for changes in therapy price due to competition and generic entry for all treatments, as these changes in price routinely occur and can be estimated with some degree of reliability.

4. ICER's plan to seek collaboration opportunities for RWE generation is vague, does not explain the stakeholder engagement process, and does not explain specifically how RWE would be used.

Alnylam welcomes ICER's plans to include additional RWE in reviews of new treatments; however, the current value framework document is unclear on how this new process will be undertaken.

Recommendation

- We request that ICER better detail the specific types of RWE to be included (e.g. adherence information, data on unmet need, disease burden, etc.), explain the formal process to engage with stakeholders, standardize the types of RWE that are requested for modeling purposes, and explain how the RWE will be included in the review. In addition, ICER should explain under what circumstances RWE will be generated (e.g., single arm trials, new indications, when specific limitations of clinical trial data are present).

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.

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AMGEN COMMENTS ON ICER'S PROPOSED CHANGES TO THE 2020 VALUE ASSESSMENT FRAMEWORK

OVERVIEW

Amgen appreciates the opportunity to comment on ICER's *2020 Value Assessment Framework Proposed Changes*. Our comments support the Framework's evolution to align with scientific best practices and the relevant science-based, patient-centered foundational goals ICER itself has set forth. Amgen is a value-based company, deeply rooted in science and innovation to transform new ideas and discoveries into medicines for patients with serious illnesses. We hope ICER will carefully consider and incorporate our recommendations in an effort to achieve its aspiration of a more sustainable healthcare system for all patients.

We support the below goals ICER has stated for its Framework, and the current comment period presents an opportunity for ICER to deliver on these goals with aligned processes and methods:

- **Support fair pricing, fair access and a sustainable platform for future innovation.** *"Ultimately, the purpose of the value assessment framework is to form the backbone of rigorous, transparent evidence reports that, within a broader mechanism of stakeholder and public engagement, will help the United States evolve toward a health care system that provides fair pricing, fair access, and a sustainable platform for future innovation."*¹ In order to provide reports that are systematic, objective with clear guidance matched by results that are transparent, reproducible, credible and rigorous, ICER must adhere to the fundamental tenets of independence and objectivity, with greater balance between access, innovation and pricing.
- **Align healthcare services with their true added value for patients and enable patient-centered care.** *"The framework also is intended to support discussions about the best way to align prices for health services with their true added value for patients."*² While drugs represent approximately 14-17% of healthcare expenditure,^{3,4} health services including hospital, physician and clinical services represent more than half (53%).⁵ A broader focus on all health goods and services (not just drugs) will better enable ICER to inform healthcare value and sustainability.
- **Reflect the experience and value of patients.** *"Even with its population-level focus, however, the ICER value framework seeks to encompass and reflect the experiences and values of patients."*⁶ Greater patient involvement in all parts of the assessment process, such as a long-term assessment that includes the patient perspective and enables patients to vote on treatment benefit, better represents the patient value. These require accounting for well-known and recognized gaps in patient data and disease epidemiology and inequalities in available treatments, access and ability to achieve a general level of good health.

Amgen's main comments on ICER's Framework are below and detailed in the sections that follow:

- 1) **Incorporate changes to ICER's Independent Voting Panel composition and voting format to be more representative and accountable to those impacted.**
- 2) **Include and quantitatively account for all relevant value elements and perspectives, including cost, cost savings and outcomes relevant to patients and their caregivers**
- 3) **Actively incorporate Real-World Evidence with greater weighting in the assessments**
- 4) **Include Adaptations for Rare Populations and maintain for Ultra-Rare Populations**
- 5) **Strive for processes and methods that are contextually appropriate for the US and avoid importing ex-US approaches based on different social and economic systems**

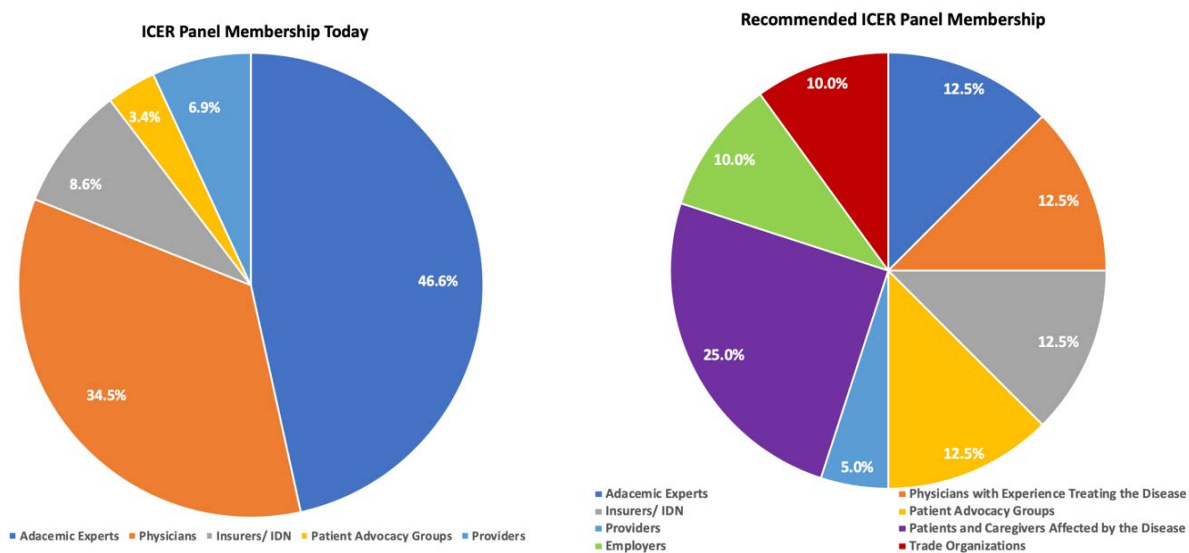
1. VOTING PANEL COMPOSITION AND DELIBERATION PROCESS

Incorporate changes to ICER's Independent Voting Panel composition and voting format to be more representative and accountable to those impacted.

ICER's Independent Panels should be representative and accountable to those that they impact with a meaningful representation in the areas of at least 15-20% of the panel discussants and votes. Anything less than this, risks continuing the current perception that ICER decisions are imposed on the most poorly represented group with the largest stake in the outcome. Past, present, and future patients and those who pay premiums to protect themselves in the event of disease pay for nearly all of health care through their taxes, wage concessions, copays, premiums, and out of pocket cash payments. Insurance companies, health care providers, manufacturers, policy makers and scientists are essentially trustees for the former group. With this in mind, people with an intimate connection to health care consumption for the ICER disease area at hand should have much more representation on voting panels that inform value recommendations than the current 3%.

While ICER's decisions have the largest patient impact, patients have the smallest voice across all panels and no representation on the Midwest CEPAC panel. Of the 58 members across ICER's CTAF, New England CEPAC, and Midwest CEPAC panels, (19, 21, and 18 respectively), 47% is composed of academics, 34% physicians (all MDs that are not providers, public health/ health policy experts, payers, or epidemiologists), 9% payers and IDNs, 7% providers, and a mere 3% from patient advocates (Figure 1). At present, votes on value that could impact hundreds of thousands of patients are determined by less than 20 people lacking representative diversity to the populations they impact.

Figure 1: ICER Panel Membership Today & Recommended Membership



Amgen appreciates ICER is taking steps to optimize the conduct and deliberation of its panels with a Code of Conduct and encourage ICER to refine and enforce this new mandate. ICER should continue to use the code of conduct to ensure the perception of professionalism and objectivity during discussions and voting. In particular, ICER staff should be especially wary of influencing the relatively less expert panel members through leading questions, condescension (albeit inadvertent), failure to adequately justify and explain findings and provide counterpoints and disconfirming information, or statements that question or influence panel members voting. The code of conduct should equally apply to panelists, participants and the meeting moderator/facilitator. The moderator/facilitator, including Panel Chair, plays an important role in anchoring the discussion, framing the questions and guiding the votes, which needs to be managed as objectively as possible.

ICER's lay-friendly seminars that provide background on evidence-based medicine to aid in assessments and better engage stakeholders should be led by external experts and patient advocates.⁷ We commend these seminars overall but more should be done to make them even more responsive to underrepresented stakeholders. ICER should allow patient advocates to lead these webinars to ensure patients gain a voice and are able to communicate their needs and priorities when voting on value for various diseases. ICER should consider collaborating with the National Health Council (NHC), who have specifically developed a tool to evaluate and maximize patient centeredness, the NHC Rubric to Capture the Patient Voice.⁸ This tool focuses on seven domains of patient centeredness: 1) Patient Partnership, 2). Transparency, 3). Representativeness, 4). Diversity, 5). Outcomes patients care about, 6). Patient-centered data sources and methods; and 7). Timeliness. Central to this Rubric is the co-development of solutions where patients are recognized as equal partners.^{9,10} ICER should consider applying this Rubric to ensure that patients and advocates do not feel like passengers in this process, but are active participants in developing appropriate methodology to assess treatment value and its implementation for each individual assessment ICER undertakes

2. PATIENT VALUE AND CONTEXTUAL CONSIDERATIONS

Include and quantitatively account for all relevant value elements and perspectives, such as cost, cost savings and outcomes relevant to patients and their caregivers

ICER should consistently incorporate the full disease burden to more holistically reflect the impact of a new health technology in alleviating this burden and improving overall health and economic outcomes. Disease burden includes the burden of out of pocket costs, lost productivity, emotional distress, and overall financial stress to the patient, their caregivers, families, and wider communities including employers, and society as a whole. Relevant stakeholder cost savings include non-medical costs, such as patient and caregiver out-of-pocket costs, lost productivity costs and impact on the health and wellbeing of caregivers and families. These should be included in a reference case, as is recommended by the 2nd Panel on Cost-effectiveness in Health and Medicine, which directs the capture of family and caregiver impacts.¹¹

ICER's Framework should actively supplement the QALY and evLYG, synthesizing the value from all relevant contextual elements and criteria and reflecting it in the numerical output of its analysis. ICER risks the integrity of its appraisal process by placing false precision on QALYs and willingness to pay (WTP) thresholds. QALYs elevate utility maximization above all other principles and are therefore a very rough and imperfect starting point for health care allocation. We don't stop treating the very ill and dying in the US once they cross some arbitrary threshold for

acceptable utility gains. evLYG is a good start towards looking at a broader range of alternatives, but this is utility by another name, and is not so different from the QALY in either principle or magnitude.

Until more measures gain familiarity and acceptance that reflect the additional values of equity, societal preferences, and other non-utility-based techniques, the QALY can be used as a starting point for HTA assessments, but assessment should not stop there. Research suggests that a flexible application of the QALY, including supplementing it with other elements of value, can help to account for its limitations in circumstances where a QALY is used.^{12,13,14} QALYs fall short in measuring small but meaningful health status changes, they are difficult to measure in those who cannot speak, are too young or very old and further QALYs are inconsistent across patients.¹⁵ ICER had previously experimented with a modified multi-criteria decision-analysis (MCDA) approach and should secure learnings from that experience with expert input to inform alternative approaches to robustly incorporate additional data with relevant weights.¹⁶ This is an evolving field and despite prior attempts to incorporate MCDA or other alternatives,¹⁷ a flexible, iterative approach may be needed until best practices are defined, enabling early patient preference and expert input to inform weighting across therapeutic areas, with full transparency.

ICER should engage in a stakeholder-driven deliberative process where all value elements are presented and considered by the panel *before* the vote on long-term value for money. While ICER panels vote on contextual considerations and other factors, ICER's threshold guidance in deliberations translates to an insignificant role for these considerations. Part of the challenge is that stakeholder testimonials and other considerations are presented after the long-term value for money assessment has already taken place, and the Panel voting is guided by explicitly stated thresholds and quantitative values, which do not reflect alternative and potentially more expansive versions of valuation. This results in a vote solely determined by the quality adjusted life-year (QALY) with value empirically driven down by ICER's guidance and restrictions.

Before 2016, QALY and threshold driven 'low-value' criteria were much less rigid. Pre-2016 ICER panels with more flexibility deemed seven out of 20 ICER drug assessments during this period, which came above the \$150,000 threshold, as of largely intermediate value.¹⁸ With current ICER assessments, the opportunity for the panel to use additional evidence and considerations to vote on value for those treatments that are not ultra-rare and come above ICER's 150,000 +25,000 threshold is impossible in practice. ICER should enable the voting panel to deliberate based on all available value elements (which should be incorporated early on in the assessment) and eliminate the automatic 'low value' (to payer) rating for values above the ICER threshold. This will enable ICER to secure a more equitable, informed, accurate and independent (albeit still estimated) vote on value.

3. REAL-WORLD EVIDENCE (RWE)

RWE should be fully incorporated in future ICER assessments, including adjustment of RCT data where appropriate

We appreciate ICER's stated intent to leverage RWE data for new analyses to address key evidence gaps and strongly urge ICER to *fully incorporate* these data in its assessments.¹⁹ This includes adjusting the Evidence Rating Matrix with clearer guidance to accommodate greater availability of RWE and provide equal consideration with RCT data. As a fundamental principle, skillful health economics uses a majority of the data available to continually inform and modify estimates of the cost and outcomes of disease. Unless modified in its revised Framework, ICER's

current approach remains at high risk of imprecision and errors as it discards over 99% of data because it does not fit their criteria of “acceptable.” For a more accurate analysis, ICER must be willing to modify base randomized trial data with RWE estimates of disease prevalence, event rates, treatment use, population demographics, and other attributes of real-world clinical practice that provide a more relevant assessment of a new technology applied in a population health setting. Historically, ICER's assessments have defaulted to clinical trial data over consideration for real-world data, selectively using RWE where clinical data were not available.²⁰ Full incorporation of RWE in HTA assessments with greater weights provides a more holistic approach to healthcare cost sustainability. Payers already do this using actuarial analyses that account for differences between their insured population and data from other populations and treatment settings. ICER should be using RWE in this way as well. (Please see Appendix for additional supporting examples).

When analyzing uncertainty to guide panel deliberations, ICER should simulate only plausible scenarios instead of pre-specified analyses and adjust uncertainty over time with RWE. ICER proposes adding a new sub-section to voting, titled “Controversies and Uncertainties”, to explore conservative or optimistic model variations to acknowledge uncertainties and controversies raised by various stakeholders, while lending greater transparency to the rationale behind methodological decisions that underpin the base case.²¹ Typically reliant on modelling, ICER simulates treatment impacts over years, even decades; a process reliant on highly simplified use cases, structural assumptions designed to reflect future clinical practice and cost and efficacy assumptions derived from clinical trials, epidemiological studies and secondary sources. The amount of uncertainty can be staggering in an assessment and can never adequately be addressed by sensitivity or scenario analysis, which necessitates consistent and ongoing validation with real-world evidence.

ICER's assessment timeline should account for RWE in support of its stated commitment to perform and incorporate relevant *de novo* data analysis, yielding more accurate results.²² Given increased availability, accessibility and speed of analysis, ICER has an opportunity to collaboratively incorporate relevant RWE analysis with relevant timeframe extensions. Similar to ICER's proposal to increase assessment timelines for large drug class reviews,²³ provisions should be built in that specifically addresses increasing the timeline necessitated to incorporate RWE that more accurately reflects the changing treatment paradigm. This is particularly important in areas for special populations such as pediatrics, rare disease and other vulnerable groups where accurate data representative of real-world clinical practice regarding disease process, disease state, QALY values and natural disease history are otherwise not available or are rapidly evolving.^{24,25,26}

4. RARE, ULTRA-RARE & SPECIAL PATIENT DISEASE POPULATIONS

Include Adaptations for Rare Populations and maintain for Ultra-Rare Populations

Treatments for rare diseases should not be evaluated with the same value assessment framework as for common drugs. It is wrong to impose a pure utilitarian approach over the empirical economics of health care which attempts to justify a rigid threshold for utility-per-life-year-per-person, especially for rare disease. ICER states that there are “*important equity concerns related to extending the threshold range higher for treatments just because they treat a small population*”,²⁷ but higher resource inputs for a minority is exactly the principle of insurance in general. Over a lifetime, most people pay more in insurance than they ever recover in paid benefits precisely because utility varies from person to person, disease to disease, with the truly unlucky receiving greater benefits. Rare diseases generally require the same degree of societal ingenuity, resources, and effort

to develop new treatments or cures as common diseases, and the elevation of acceptable utility-per-life-year-per-person allows society to engage in these pursuits for the rare and unlucky. Patients with rare disease are born with inherently diminished chances of a healthy life compared to the general population – they lack the ‘fair innings’ of the majority of individuals.²⁸ The equity concern that ICER describes for special treatment for a small population is intrinsic to the argument in that rare diseases do need to be assessed more discerningly and carefully than common diseases such as stroke or migraine.

Aggravating the imperfection of the QALY is rigidity regarding “thresholds”, which are particularly inappropriate for rare diseases. Patients with relatively rare illnesses, defined presciently by the FDA decades ago and still relevant today as starting at <200,000 cases nationally, are particularly disadvantaged when monolithic thresholds are applied.²⁹ Defining the new standard of “rarity” as 10,000 or less is uncoupled from the reality of the larger per-patient investments required by government, industry, and society if we have any interest in equity towards those who are not fortunate enough to have a “common” disease. ICER should adopt accepted health economic practice which avoids providing a single, falsely precise answer to decision makers where there is inadequate knowledge to question it appropriately. ICER should also eliminate the 10,000 person threshold for rare disease until more objective research is available to quantify the relative increase in per-patient investments that are required for innovation in a given rare disease area. In ICER’s 2020 Framework, a standardized cost-effectiveness threshold will be used, from \$50,000 to \$200,000 per QALY/evLYG, for all diseases, from common to ultra-rare.³⁰ If a threshold must be used, then it is becoming widely recognized that rare and health-catastrophic conditions should be judged against a higher threshold.³¹ A common threshold is not appropriate for rare diseases as these diseases are by their very nature, uncommon. In addition, the \$200,000/QALY upper threshold can be expected to constrain access to rare disease treatments in the absence of published literature. 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. At a time when fewer than 5% of the >7,000 recognized rare diseases globally still lack a viable treatment,³² 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 rare disease patients and their families. The updated Framework should align with the definitions and provisions in place to protect patients with rare diseases, including accommodation for the difficulty in designing, recruiting, and performing clinical studies.

ICER should change the Evidence Rating Matrix used for voting to reflect common or rare and ultra-rare disease prevalence categories. A fundamental issue with the guidance the voting panel receives on net health benefit is that the same Evidence Rating Matrix is used for common diseases as for rare disease despite the well-known challenges associated with collecting data, recruiting and performing clinical trials and unknowns in the natural history, epidemiology, diagnosis and treatment of rare and ultra-rare disease. Also, the current approach places ICER out-of-step with the US regulatory framework, as the FDA relies on the ODA for its orphan designation.³³ As suggested by HTA experts,^{34,35} ICER should accommodate for this critical area of difference in their preparation and rating of clinical benefit, which can have a profound impact on voting results. Moreover, ICER must consider the need for breakthrough therapies that the FDA has deemed of public interest to approve when accounting for uncertainty in evidence. Any breakthrough therapy that has received accelerated approval and or priority review from the FDA will often have limited clinical data with minimal long-term outcomes available. ICER should take into consideration that rare therapies will by their very nature have extensive uncertainty. Similar to changes in the voting and deliberation processes that ICER applies to ultra-rare disease treatments, ICER’s Evidence Rating Matrix should

be updated to reflect well acknowledged limitations in rare and ultra-rare disease and look to global HTAs for reference.^{36,37}

5. U.S. CONTEXTUALLY RELEVANT METHODS AND PROCESSES

Strive for processes and methods that are contextually appropriate for the US and avoid importing ex-US approaches that are based on different social and economic systems

ICER should not adopt or map to foreign health technology assessment systems, as these are based on an entirely different healthcare environment than the US. ICER proposes to reference its evaluation of the evidence for added clinical benefit with the *rating system* used in Germany. While every HTA system has its strengths and weaknesses, they are designed to address the needs and constraints of the social and economic infrastructure within which they reside. Moreover, the considerable variation in HTA agency assessment of evidence demonstrates how context is fundamentally anchored to the empirical application of these techniques. The US healthcare ecosystem is a complex, multi-payer system with an inherently different infrastructure and context than Germany. In the German system, IQWiG provides a recommendation on the benefit at the request of the G-BA; however, in the end the G-BA makes the final decision which can differ from the IQWiG recommendation. Two separate studies demonstrate considerable variance in the evaluation of additional benefit for drugs in early benefit assessments (EBA) between IQWiG and the G-BA.^{38,39,40} While there may be opportunities to consider high level principles from other HTAs, it is critical to note that every HTA has its limitations and challenges, and the specific methods and processes employed by ICER must be contextually grounded to the US system. ICER's step in evolving the way it rates evidence is important to securing wider applicability and acceptance of assessments, but any HTA technique must be designed to address internal validity, context, accuracy and flexibility in addressing the diverse needs not only at a national level but for individual communities.

CONCLUSION

Budget holders, decision makers and the stakeholders impacted by assessments can benefit if ICER focuses on key pillars of evidence, robust analytics, and the identification of areas of uncertainty. Health technology assessment should always be accompanied with a reasonable consideration of how Framework methodology impacts improvements in health delivery and overall healthcare outcomes.^{41,42,43,44,45} Thoughtful attention should further be given to the fact that at any given time we are all patients who will likely feel the impact of ICER's assessments. Amgen appreciates ICER's engagement of stakeholders in an effort to continuously update its Framework and urges ICER to create a 2020 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 payer decisions with a systematic approach to the evaluation of evidence with flexibility, inclusiveness, scientific integrity, transparency, and patient centricity, in the absence of absolutes.

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APPENDIX

The full incorporation of RWE requires ICER to give greater weight to this source of data, going beyond simply validating select assumptions and enabling RWE to modify key drivers and results.

Considerations of differences between RCT and RWE	Example
There are marked differences in estimates from RCT data and real world clinical practice, which has dynamic, heterogenous settings.	In the area of bone fractures in patients with cancer metastasis, RWE of higher fracture rates seen in clinical practice necessitates adjustments to clinical trial evidence in any HTA assessment. ⁴⁵
Important counter-intuitive differences with serious impact on patient outcomes can be uncovered as clinicians decide how they utilize new treatments in their practice.	E-cigarettes were assumed to increase likelihood of quitting; however, a systematic review of 38 studies showed exactly the opposite: the odds of quitting cigarettes were 28% lower for individuals who used e-cigarettes compared with those who did not. ⁴⁵
Safety can differ significantly from trials to real-world practice.	Trials in anticoagulant-naïve patients with atrial fibrillation (AF) treated with dabigatran etexilate raised concerns on bleeding events and myocardial infarction (MI); however, a follow-up registry data analysis of nearly 14 thousand patients showed bleeding rates were comparable and mortality, intracranial bleeding, pulmonary embolism, and MI were lower with dabigatran.⁴⁵ A publication of a meta-analysis of twenty-three thousand patients demonstrated a significant real-world increase in MI for rofecoxib versus placebo, leading to one of the most well-known drug withdrawals involving rofecoxib.⁴⁵
Costs can change significantly from models of long-term cost-effectiveness analysis when validated in real-life clinical settings.	In a study on the real-world practice of schizophrenia treatment, the average annual costs per patient for an atypical antipsychotic was 16% of the costs in published trials. ⁴⁵



October 18, 2019

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

Re: 2020 Value Assessment Framework Response:

Introduction

The Alliance for Regenerative Medicine (ARM) is pleased to provide our comments in response to the Institute for Clinical and Economic Review (ICER) October 18, 2019 request for inputs on the “2020 Value Assessment Framework.”

ARM is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 350 leading research-based life science companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. Our members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, as well as the submission of investigational new drug (IND) applications, and Biologics License Applications (BLA) for such products to the FDA. ARM takes the lead on the sector’s most pressing and significant issues, fostering research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

The HTA evaluation issues raised in the ICER press release raise critical concerns for ARM members. Cell and gene therapies have shown the potential to cure many diseases, some of which are partly or fully caused by genetic mutations. ARM member companies have shown convincing evidence of halting progression of severe and rare diseases in many of their development programs. Cell and gene therapies are complex to manufacture, can require custom processes to create individualized therapies, and in many cases are administered once or over a short course of treatment. While expectations are that the patient outcomes will be durable over the long-term, the payment may be incurred and settled at the time of treatment in many cases.

With the emergence of these therapies, we are entering an unprecedented era of potentially curative treatments for patients where no cure existed before. ICER has previously acknowledged, “[t]he science is undeniably exciting” and can “reflect extreme magnitudes of lifetime health gains and cost offsets that are far beyond those generated by traditional therapies.” More recently ICER has stated “[c]ell and gene therapies are starting to provide truly transformative advances for patients and their families, particularly those with conditions for which there has not been any effective treatment before.”

ARM believes that an independent scientific evaluation of the clinical and economic evidence should be conducted first, without consideration of price or payment model, in order to

understand the clinical benefits of a new technology. ARM also believes that every effort should be made to ensure patients have access to transformative new therapies in a timely manner and that incentives for innovation remain in place, so that undue challenges in market access and commercialization do not hinder the pace of innovation for this new class of transformative therapies.

In prior public statements, ARM has been clear that traditional HTA frameworks in both U.S. and Europe are not flexible enough to appropriately evaluate potential cures and do not capture the full product value due to issues including: the short term time frame for assessing affordability versus the long-term timeframe for assessing value; variability in willingness to pay based on degree of unmet medical need addressed; and the subjectivity of incorporating contextual considerations such as caregiver and societal impacts into a quantitative framework¹.

ICER states that its mission to ‘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’. US payers are increasingly relying on ICER evaluations in setting their cost-effectiveness thresholds, informing utilization controls and coverage policies and setting and negotiating price, including value-based arrangements (ICON, PLC 2019 Whitepaper ‘Current US payer’s perceptions on value-based pricing for pharmaceuticals’). In the spirit of fulfilling this mission, ARM suggests that ICER should endeavor to be as broad, inclusive and transparent as possible about its methods and assumptions, not less inclusive and transparent as suggested by the current proposed changes to the ICER value framework. One example of a proposed change to the 2020 framework in direct opposition to inclusivity and transparency is the proposed use of a narrower set of QALY thresholds in sensitivity analysis for orphan drugs. US payers have the ability and latitude to select the willingness to pay and cost perspective (healthcare system, societal) most appropriate to their own resource allocation decisions. Reducing and limiting these perspectives within value assessments and reports may reduce coverage and access to potentially valuable therapies that do not fit well into a traditional Cost/QALY framework.

In the current open comment period for the 2020 value assessment framework, ICER has solicited input on several proposed adaptations. Among these adaptations, ARM supports the following proposed changes:

- **Augment Efforts to Use Real World Evidence (RWE):** We support ICER’s effort to generate RWE for value assessments and recommend that these data be made publicly available. Additional clarification on how ICER plans to collect, analyze and use RWE, however, would be informative. Transparency will be critical here for all stakeholders.
- **Expanding and Revising Voting Structure to Capture Important Potential Other Benefits and Contextual Considerations:** The addition of other important benefits and contextual considerations will allow the ICER report audience to garner a better understanding of the quantitative impacts of a treatment that are not captured in the cost-effectiveness analysis.

¹ See March 29, 2017 ARM letter to ICER regarding the proposed update to the ICER Value Assessment Framework.

- **Creating a New Process for Re-assessing the Emergence of New Evidence:** We suggest that ICER also consider an evidence re-assessment at the 5-year mark when additional RWE is likely to be more readily available.

In addition to these areas of agreement, ARM would like to highlight several concerns with ICER's approach and proposed adaptations:

- **Timing of Review is Premature:** An important limitation in ICER's approach is in the timing of its review of new therapies, particularly those that are first in class and the only treatment for a given condition. ICER routinely schedules the release of its evaluations to coincide with anticipated FDA approval. Conducting a value assessment prior to regulatory approval denies patients, providers, and health insurers a comprehensive understanding of a treatment's potential benefits and risks. This practice is premature and limits the amount of data and information that can be incorporated into ICER's assessment and upon which ICER can base its conclusions. Post-marketing trials, such as confirmatory studies for accelerated approval drugs, and real-world evidence from registries and other data generation methodologies can provide invaluable data on a drug's benefits and risks derived from longer-term use for a more complete picture of a drug's impact. In the absence of these data, ICER evaluations begin with a premise of insufficient evidence of clinical benefit which inherently biases the review towards a finding of low cost-effectiveness. This is especially true of accelerated approval drugs in which clinical benefit is verified through post-approval trials. ICER's decision to issue its reports and identify a value-based price benchmark at the time of a drug's approval in order to influence payer decisions and launch price reflects a narrow focus on cost constraints and access restrictions. This practice is at odds with the reality that certain data are not yet available at the time of launch and the importance of obtaining such information to yield an accurate assessment of both short and long-term value which will lead to maximizing value for patients.
- **Cost-Effectiveness Threshold Ranges:** Omitting the willingness to pay (WTP) threshold up to \$500K per QALY/evLYG removes important information from ICER's reports, especially for stakeholders in the United States, where different payers will consider different WTP thresholds.^{2,3,4,5} The proposed framework will lessen incentives to develop transformative treatments for rare diseases, where it is more difficult to demonstrate cost-effectiveness using traditional WTP thresholds applicably to more

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widely used treatments.^{6,7} With this measure, ICER departs from the path taken by other global HTAs (e.g. NICE), where higher WTP thresholds are used in order to enable innovation for rare diseases.⁸ We suggest that mis-representation or mis-interpretation of the thresholds used can be mitigated by providing additional clarifying discussion in the framework document and ICER reports and statements.

ICER also states that it “*only takes \$100,000 per treatment course, multiplied by a mere 10,000 patients, to provide \$1 billion per year in revenue.*” However, many ultra-rare diseases impact fewer than 1,000 patients per year.⁹ Furthermore, uptake among patients is often far from 100% due to unique disease, treatment and patient segment characteristics and has been consistently overestimated by ICER.¹⁰ Non-oncology rare disease drugs that consistently generate more than \$1 billion in global revenues are the exception, not the rule. As the cost to bring a drug to market has been estimated to exceed \$1 billion, manufacturers will not develop new treatments if there is no way to recoup investments, leading to a high unmet need remaining for patients with rare diseases.¹¹ This will have a broad impact in the US, where 25 to 30 million people are estimated to suffer from a rare disease.¹²

Recognizing the inadequacy of traditional cost-effectiveness thresholds for rare disease and transformation products, NICE has adopted an innovative way of incorporating QALY weightings that have the effect of adjusting cost-effectiveness thresholds for therapies targeted for rare conditions through the Highly Specialized Technologies pathway (meeting certain criteria, including small eligible patient population and minimum QALY increases).¹³ The minimum QALY criteria ensures that only therapies with substantial health benefits in rare diseases will be evaluated using the higher thresholds.

- **Contextual Considerations should be considered in calculating Value-Based Price when possible.** While we agree with ICER that including contextual considerations is important, these broader benefits typically do not influence ICER’s recommended value-based price. For instance, one can readily calculate the value of reductions in caregiver burden and using approaches similarly to those used to estimate treatment impact on

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¹¹ Adams CP, Brantner VV. Spending on new drug development 1. Health economics 2010;19:130-41.

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patients' quality of life.^{14,15} These additional components of value can be calculated in many cases and may significantly impact a treatment's cost per QALY.¹⁶

- **Include an Undiscounted Approach as a Sensitivity Analysis.** While discounting is common in cost-effectiveness modelling, this approach may undervalue treatments which have large health benefits that accrue into the future. Aggressive discounting can sometimes make common-sense public health interventions appear to be of low value.¹⁷ In some cases, discounting can lead to unreasonably low valuations that undervalue transformative innovations, a result that is at odds with society's stated preferences.¹⁸
- **Applying More Precise Evidence Ratings:** The proposed evidence rating matrix is unclear and subjective, and the voting record demonstrates a lack of consensus and clarity on the meaning of the ratings. The ICER framework has two dimensions of assessing the evidence: 1) level of certainty and 2) comparative benefit. We would recommend developing explicit measures for drivers of both certainty (e.g. trial size, active comparators, randomized clinical trials, single arm trials, meta-analysis etc.) and comparative benefit (e.g. relative efficacy, AEs, net clinical benefit, etc.).

Additionally, it should be noted that surrogate endpoints used in FDA's accelerated approval pathway are not adequately accommodated for in ICER's framework when reviewing drugs that receive FDA approval through this important expedited program. The accelerated approval pathway represents a pragmatic approach to addressing the challenges and limitations presented by small, difficult to study patient populations, allowing for flexibility in the types of evidence that can be used to satisfy the full statutory standards for safety and effectiveness that apply to all drugs approved by the FDA. The key challenge in applying ICER's framework to accelerated approval drugs lies in the fact that the full extent of clinical benefit has not been established at the time of approval and it can take years to verify the anticipated clinical benefit in post-approval confirmatory studies. As Drs. Woodcock and Marks recently reinforced, accelerated approval "is especially useful when the drug is meant to treat a disease whose disease course is long, and an extended period of time is needed to measure its effect"¹⁹ (August 27, 2019, FDA Voices).

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¹⁷ NICE CC. How Should NICE Assess Future Costs and Health Benefits? 2011.

¹⁸ Bonneux L, Birnie E. The discount rate in the economic evaluation of prevention: a thought experiment. *Journal of Epidemiology & Community Health* 2001;55:123-5.

¹⁹ FDA. Delivering Promising New Medicines Without Sacrificing Safety and Efficacy. FDA Voices: Perspectives From FDA Leadership and Experts. August 2019. Available at: <https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/delivering-promising-new-medicines-without-sacrificing-safety-and->

- A Crosswalk Between ICER Evidence Ratings and Those of the German HTA System not currently suitable for US health technology assessments:** Although Germany is the largest pharmaceutical market in Europe, the German system for evidence rating has not been established as a uniformly and internationally accepted standard for evaluating evidence.^{20,2119,20} We question the need to use the German system before an international standard has been set. We also find ICER's proposed crosswalk to the German evidence rating system to be unclear and subjective. For example, evidence rated an "A" in ICER's EBM matrix could be either "major" or "considerable added benefit" in the German system. Further, if ICER's EBM matrix rates evidence as either C+, C++, P/I, C, or I, then it would be considered to have "no added benefit proven" when cross-referenced to the German rating system, despite ICER's own assessment that these treatments have value. ICER states they will *"provide [their] own judgement of 'added benefit' within the German categories... rather than rate the evidence in the same manner as would be done in Germany."* Using the ratings of the German system without implementing the methodology they were designed for is inconsistent and makes assessment of the ratings difficult, confusing, and ultimately incompatible with the actual results of German HTAs.

ARM appreciates the opportunity to provide our perspective on these important issues. Please do not hesitate to contact me if you have any questions.

Sincerely,



Robert J. Falb
Director, U.S. Policy and Advocacy

[efficacy?utm_campaign=Delivering%20Promising%20New%20Medicines%20Without%20Sacrificing%20Safety%20and%20Efficacy&utm_medium=email&utm_source=Eloqua](https://www.icer.org/efficacy?utm_campaign=Delivering%20Promising%20New%20Medicines%20Without%20Sacrificing%20Safety%20and%20Efficacy&utm_medium=email&utm_source=Eloqua). Accessed October 8, 2019.

²⁰ Mycka J, Dellamano R, Lobb W, Dellamano L, Dalal N. Orphan drugs assessment in Germany: a comparison with other international HTA agencies. *Value in Health* 2015;18:A550-A1.

²¹ Schaefer R, Schlander M. Different Methods, Different Results? Comparing Health Technology Assessments in the United Kingdom and Germany. *Value in Health* 2016;19:A494.

October 18, 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: Updates to 2020 Value Assessment Framework Methods and Procedures

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's) proposed updates 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.

We appreciate ICER's commitment to regularly updating its value framework methodology and process. That these updates are necessary points to the evolving and ongoing discussion around how best to measure value in health care interventions.

BIO has commented previously on updates to ICER's value framework methodology, and most recently on proposed changes to the framework for when ICER assesses single or short-term transformative therapies (SSTs). Throughout these comment letters, we have emphasized the need for substantive changes to ICER's methodology and process to more accurately describe the value of the therapy under review. In our comments submitted to ICER on June 10, 2019, we recommended ICER prioritize modifications that would ensure 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."

Unfortunately, the modifications ICER has proposed in its update for 2020 fail to correct these deficiencies. Some of these changes – such as the inclusion of new sections on "controversies and uncertainties" and patient perspectives – are certainly steps in the right direction. However, ICER's reports would continue to provide stakeholders with a view of value that is at best incomplete, and at worst inaccurate.

We strongly recommend ICER revisit its proposed modifications to its value framework along these principles. As part of this reassessment, we encourage ICER to consider the following specific recommendations:

Transparency

One theme we have consistently raised with ICER is the lack of transparency into its model and process. While ICER has made some effort to address these concerns, we believe some of the changes proposed in the updates for 2020 work at cross purposes with the goal of providing more transparent value assessments. For example, in this update ICER has proposed several changes that favor one type of information over another (e.g. discounts vs. non-discounted results, societal vs. health system perspective).

The decision to exclude certain measures or data points because ICER is concerned with how such information is "perceived" is antithetical to the idea of a fully informed and open debate about the value of a health intervention. Providing information on discounted and undiscounted costs, for example, does not imply an endorsement of one approach over the other. Rather, it provides greater transparency to stakeholders about whether discounting greatly impacts the assessment's results and allows them to choose for themselves which approach makes sense in context. ICER should strive to include all relevant measures, explain the advantages and disadvantages of each, and allow the readers of its reports to decide which are the most pertinent to their decision-making process.

Standardized Cost-Per-QALY Thresholds

In these proposed modifications, ICER would adopt a common set of cost-effectiveness (CE) thresholds across assessments for all products – including those that treat ultra-rare diseases. We have significant concerns with this approach. When ICER adopted its modified framework for treatments for ultra-rare conditions, we strongly supported broadening the willingness-to-pay threshold for these therapies. We also recommended ICER expand its value-based pricing benchmark for these treatments to better reflect their long-term value.

The proposal to use standardized CE across all assessments is a dramatic step backward from the goal of providing holistic value assessment. Such a change could have the unintended consequence of penalizing manufacturers for investing in the research and development

necessary to develop the next generation of treatments for rare disease. New therapies for rare diseases face more significant hurdles in establishing CE using traditional thresholds due to the nature of developing a drug for a small patient population. Utilization of a static threshold fails to recognize the contextual nuances inherent in the rare drug development process and could ultimately limit patients' access to lifesaving treatments.

We strongly recommend ICER consider alternative methods outside of the establishment of rigid CE threshold ranges in order to address the concerns ICER outlined in the draft changes. Additionally, and as we have commented previously, we recommend ICER work with patients representing rare disease communities to ensure that the methods adopted conform to those elements of value that are of greatest importance to the patients themselves.

Premature assessment of new therapies

As we have commented previously, we disagree with ICER's conducting assessments that have yet to receive, or have only just received, approval from the Food and Drug Administration (FDA). This is a critical limitation of ICER's approach to conducting value assessment. Conducting a value assessment prior to regulatory approval denies patients, providers, and payors a comprehensive understanding of a medicine's potential benefits and risks. This practice is premature and limits the amount of data and information that can be incorporated into ICER's assessment and upon which ICER can base its conclusions.

Conducting value assessments on products that have just come to market also biases studies against drugs that have utilized the FDA's accelerated approval pathway. These drugs' clinical benefit is verified through post-approval trials, real-world evidence from registries, and other data generation methodologies. These studies can provide invaluable data on a drug's benefits and risks over a longer time horizon for a more complete picture of a drug's impact. In the absence of these data, ICER evaluations begin with the premise of insufficient evidence of clinical benefit, which inherently biases the review towards a finding of low cost-effectiveness. This practice is at odds with the reality that certain data are not yet available at the time of launch and the importance of obtaining such information to yield an accurate assessment of value to the patient. In the final modifications, we encourage ICER to conduct its assessment only after sufficient time has elapsed for these key data elements to be captured.

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



October 18th, 2019

Dear Dr. Steve Pearson,

Thank you for the opportunity to comment on ICER's Proposed Changes to the 2020 Value Assessment Framework. Our comments below add to those we submitted on the 6th of September 2019 with regards to the proposed adaptations to the SST Value Assessment Framework. We believe those comments are also relevant for consideration as part of the proposed 2020 Value Assessment Framework changes.

The proposed changes to the 2020 Value Assessment Framework address several important assessment issues; however, Biogen continues to believe that the current framework is too heavily reliant on the point-estimate conclusions of formal cost-effectiveness analyses. We recommend that continued efforts focus on developing a broader and more transparent value framework that goes beyond the QALY and encourages best practice evidence generation.

Additional comments and recommendations:

Extending the Value Framework

Biogen continues to have concerns about the limitations and use of the QALY within the Value Assessment Framework. We have highlighted in previous responses that QALYs do not adequately capture the wide variety of benefits that a successful therapy can achieve, including a person's return to economic productivity, their performance in school, ability to function as a caregiver for others, and so on.

The proposed changes to the 2020 Value Assessment Framework are a pragmatic response that attempts to address limitations associated with a narrow focus on cost-effectiveness. ICER's introduction of additional elements of value to the framework and the adoption of a Likert scale voting format acknowledge the current limitations. These advances are essentially divorced from the current assessment framework as they are not incorporated in any quantitative way to the cost effectiveness estimates and subsequently do not meaningfully inform a value-based price.

This disconnect between cost-effectiveness modeling and the qualitative assessment of additional elements of value has important implications, particularly for future assessment transparency. ICER has previously considered adopting a formal MCDA process. However, the current proposal is a modified approach in which factors are voted upon but not formally incorporated into the quantitative assessment. Biogen recognizes the challenges with a formal MCDA approach, however, there needs to be a more transparent mechanism for incorporating or weighting value impacting elements into the estimation of a value-based price assessment.

Best practice evidence generation

Incentivizing best practice evidence generation must be a key objective underpinning ICER's Value Assessment framework. In our response to the SST adaptations proposals, dated September 6, 2019, Biogen emphasized the need to revisit the current Evidence Ratings Matrix to ensure that strength of evidence is adequately captured and consistently evaluated in ICER assessments. We highlighted our concerns that in recent assessments, trials of significantly differing quality (i.e. an open label, single arm non-randomized trial versus an RCT) have been given the same evidence rating and that ICER's cost effectiveness analyses do not appropriately capture the uncertainty resulting from a reliance of low-quality clinical evidence. For example, recent evidence reports in 2018 assigned Phase III RCTs evidence ratings of C+ to B+ whereas a Phase I open-label study received an evidence rating of A for an SST.¹

The proposed changes in ICER's 2020 Value Assessment Framework to the Evidence Ratings Matrix, while welcomed, do not adequately address key concerns Biogen has regarding evidence generation and evaluation of quality. Our recommendation is that there is better discrimination of the strength of evidence relating to clinical data, including issues such as study design and numbers of patients.

Discounting

ICER proposes not to present sensitivity analyses on different discount rates as it believes that this analysis would not provide additional information that is useful to decision-makers. We believe that this should be reconsidered. There is ongoing debate on this issue and an understanding of the impact of differing rates should be made transparent to users of ICER analyses. ICER's evaluations are increasingly referenced internationally and compared to reviews conducted by ex-US HTA bodies. As with the inclusion and comparison of the German Additional Benefit Rating scale to the ICER Evidence Ratings Matrix, the presentation of a limited number of sensitivity analyses relating to discount rates would provide added value to the consumers of ICER assessments.

Biogen thanks ICER for the opportunity to comment on the proposed changes to the 2020 Value Assessment Framework. We would be happy to discuss any of the outlined concerns in more detail if needed.

Sincerely,

Chris Leibman
Sr. Vice President, Value and Access, Biogen

¹ Institute for Clinical and Economic Review (ICER). Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value. Final Evidence Report. 24May2019; Institute for Clinical and Economic Review (ICER). Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. Final Evidence Report. 4October2018; Institute for Clinical and Economic Review (ICER). Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value. Final Evidence Report. 14Feb2018.

October 18, 2019

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

Re: Comments on 2020 Value Assessment Framework Proposed Changes

Dear Dr. Pearson:

On behalf of BioMarin, I appreciate the opportunity to comment on the Institute for Clinical & Economic Review (ICER)'s proposed changes to its value framework adaptations for 2020. BioMarin is a global leader in developing and commercializing innovative therapies for patients with life-threatening rare and ultra-rare genetic diseases. We appreciate ICER's efforts to appropriately consider the full set of benefits that ultra-rare disease therapies provide to patients, their families, the healthcare system, and society. Appropriately and fairly defining clinical and cost value is critical to ensuring patient access to life changing therapies for rare disease patients with high unmet medical need and significant potential to achieve improved health outcomes. The purpose of this letter is to provide our perspective and input on select proposed changes to ICER's value framework for 2020.

Evidence-rating matrix. ICER should adjust its expectations for quality of evidence and employ greater flexibility to consider inclusion of lower quality levels of evidence for ultra-rare disease therapies, including pragmatic approaches to comparative data, case studies and small case series of few patients. Additionally, ICER should clarify how clinical evidence on treatments for ultra-rare disorders can be appropriately considered given the significant benefits gained by patients, the healthcare system, and society.

ICER's evidence rating matrix does not adequately consider evidence generated for therapies in ultra-rare diseases. In clinical trials of therapies being investigated for ultra-rare diseases, manufacturers are often developing a therapy while trying to better understand the natural history of the disease, disease burden, and how to measure the impact of a new treatment – especially for those therapies that are the first to be approved for a respective disease state or indication. The relevant evidence base from clinical trials for ultra-rare disease therapies can rely on smaller studies of a lower level of evidence, due to challenges with conducting more robust clinical trials. Challenges include limited capabilities to obtain control data or data to inform on the natural history of the disease, such as diagnosis challenges, ethical challenges with developing control data for invasive therapies, or withholding a potential therapy from patients without therapeutic alternatives.

ICER's rating scale may not preclude evidence for ultra-rare disease therapies from being categorized as 'Promising but Inconclusive' (P/I). Further, such disease states and therapies often have limited real-world evidence to support assessments due to aforementioned limitations of research and incomplete understanding of disease state. Such limitations preclude our understanding on which clinical assessments and recommendations sufficiently relay the full set of benefits patients can gain from therapies, and limit patient access to treatment.

Cost-effectiveness thresholds. ICER should maintain the existing upper limit of \$500,000 per quality adjusted life year (QALY) for cost-effectiveness assessments of ultra-rare disease therapies to support appropriate assessments of value.

ICER is proposing to provide cost per QALY results at \$50,000, \$100,000, \$150,000 and \$200,000 for all assessments, including for treatments for ultra-rare disorders. ICER has previously acknowledged the need for ultra-rare disease therapies meeting certain criteria to require special considerations in HTA including with cost-per-QALY thresholds.¹ This position has been implemented in ICER's current value framework, which utilizes a \$500,000 per QALY upper limit for cost-effectiveness analysis of ultra-rare disorders.

ICER's proposal for the 2020 value assessment framework is in direct contrast to its previously stated positions that supports a higher cost per QALY threshold for ultra-rare disorders.² Such treatments require a higher threshold, including an ultra-rare prevalence of eligible patient population; considerations for manufacturers to recoup return on investment and incentivize innovation; and, the fact that ultra-rare therapies can often be the first available US Food & Drug Administration-approved therapies for patients addressing a significant unmet medical need. ICER's proposal to reduce the upper threshold for cost-effectiveness analysis for ultra-rare disorders from \$500,000 per QALY to \$200,000 per QALY is further misaligned with well-established ultra-rare HTA assessment methods in other countries, e.g., the distinct ultra-rare review processes in England, Scotland, and Wales. A system-wide use of inadequate thresholds could be a disincentive for innovation, and ICER should not contribute to the value discussion based on this premise.

Value-based price benchmarks. In line with comments to continue use of the \$500,000 per QALY threshold for cost-effectiveness analyses of ultra-rare disease therapies, ICER should use the \$500,000 per QALY threshold to make corresponding value-based price recommendations.

ICER is proposing to continue using the range of \$100,000-\$150,000 per QALY (as well as per equal value of life-year gained) as the standard threshold for value-based price recommendations for all assessments. These thresholds continue to be inadequate for ultra-rare disease therapies. Following aforementioned challenges with conducting research in rare disease, maintaining a viable commercial business model is critical to ensure continued research & development investment (for which much of the research is conducted by US companies) in addition to incentives for research and development of new therapies for ultra-rare patient populations who do not have other meaningful treatments. Having an appropriate threshold is critical to ensure value is appropriately assessed. Further, divorcing a value based-price from the appropriate cost per QALY threshold diminishes validity of the cost-effectiveness assessment as well as overlooking the value the therapy provides in understanding and managing ultra-rare diseases with significant unmet medical need where none or few treatments exist.

¹ Institute for Clinical & Economic Review. "Modifications to the ICER value assessment framework for treatments for ultra-rare diseases." November 2018.

² Institute for Clinical & Economic Review. "Assessing the Effectiveness and Value of Drugs for Rare Conditions: A Technical Brief for the ICER Orphan Drug Assessment & Pricing Summit." May 2017.

Dr. Steven Pearson

October 18, 2019

Re: Comments on 2020 Value Assessment Framework Proposed Changes

Page 3

Budget impact. ICER should carefully consider only the targeted eligible patient population rather than a broader (e.g., prevalent) patient population for therapies to provide a more accurate estimate in budget impact calculations. Assumptions around uptake such as diagnosis, need for multi-disciplinary care, and treatment management and associated logistics, should be transparent.

ICER is proposing to expand the number of drugs retrospectively reviewed from two to five years for calculating the budget impact threshold that triggers an ICER access and affordability alert. ICER should carefully consider how to define a treatment's target patient population that corresponds with each included labeled indication, as this patient population may not be defined only by diagnosis, but by other criteria that determine whether a treatment is appropriate. This approach risks overgeneralizing the budget impact, such that it would be inappropriately overstated. Overestimating the appropriate patient population based on vague criteria will provide an inaccurately high estimate of actual budget impact, due to estimations skewed upward for each approved indication.

Other benefits & disadvantages. ICER should not only include other benefits and disadvantages in panel voting questions, but also elevate the importance of these key aspects of treatment for ultra-rare disease therapies, including single and short-term transformative therapies for ultra-rare indications.

ICER is proposing to formally include additional benefits and disadvantages of therapies reviewed in standard voting questions during the panel at a public meeting. We support ICER's ongoing efforts to consider these benefits and disadvantages of treatments that may not be adequately captured in clinical trials, including the current proposal to formalize panel votes during public meetings. We emphasize that panel voting questions should include patient-reported outcomes (PRO) and patient voice, where the voting could consider key aspects difficult to capture in clinical studies such as energy levels, pain, quality of life (QoL), treatment adherence challenges, overall health status, change in comorbidities and complications over time, and work productivity, all of which are important to consider individually and in aggregate to assess both health system and societal benefits and value.

We appreciate the opportunity to provide input as ICER continues to refine its value framework. We encourage ICER to first consider the clinical benefits that ultra-rare disease therapies can bring to patients with high unmet medical need, and implement a transparent methods-development and application process with all stakeholders.

Sincerely,



Adrian Quartel, MD

Group Vice President, Head Global Medical Affairs

BioMarin Pharmaceutical Inc.



Bristol-Myers Squibb

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

October 18, 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. Steve 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 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.



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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 Dr. Lee Newcomer in his 2014 Journal of Oncology Practice study.³ Similarly, a BMS analysis of real-world healthcare resource utilization and associated total cost of care in advanced non-small cell lung cancer found a reduction in total cost of care when comparing time periods before and after the introduction of immunotherapies.⁴ 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.^{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 A lack of focus on the entire care continuum is a disservice to informing healthcare decision making and improving health outcomes. 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. 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.

As detailed in BMS previous comments, the use of the QALY poses several significant concerns and has limited utility in real-world discussions.^{21,22,23} 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.²⁴ QALYs are also not recognized for capturing productivity well.²⁵ ICER plans to supplement QALY based analyses with an Equal Value of Life Years Gained (evLYG) analyses, however, this measure does not fully address concerns either and has its own limitations. As ICER acknowledges, the evLYG does not fully recognize the value of medications that improve quality of life. In the context



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of healthcare decision making, this inability to distinguish improvement in symptoms between interventions would also have limited utility in the real-world.

In addition, we are disappointed that ICER retains its use of arbitrary cost effectiveness thresholds. We believe a cost-effectiveness threshold based on QALYs is ill suited for application in the US setting and around the world. The US healthcare system is a complex, heterogeneous system comprised of multiple decision-makers. A one-size fits all approach 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.

ICER should 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.

Incorporate additional elements of value

BMS is disappointed to see that ICER has chosen not to incorporate additional elements of value in any meaningful way and we strongly encourage ICER to reconsider their decision to not incorporate consensus-based elements of value, such as value of hope.²⁶ The ISPOR Special Task Force on U.S. Value Assessment recommends multiple additional elements of value – productivity, adherence-improving factors, reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option-value, equity, and scientific spillovers.²⁷ This catalogue of value elements provides one of the first, truly forward looking steps in comprehensively characterizing all of the multidimensional facets of value. In addition, patient advocacy organizations recommend including patient preferences and value into frameworks despite the added complexity.²⁸ BMS believes in patient centricity and scientific objectivity. We strongly encourage ICER to strive for the same level of patient centricity and scientific objectivity. ICER argues that methods for measuring additional value elements are not well established and that further research is needed. While some elements might be challenging to measure such as productivity there continues to be research to advance elements of value that are important to



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patients, caregivers, and other stakeholders.^{29,30} In fact, expanding the analysis to multiple additional elements can have a significant impact and has been demonstrated to achieve a more comprehensive consideration of all treatment benefits and costs.³¹ Since more research on value elements has occurred since the 2017-19 value framework³² and will continue to occur, we recommend ICER reconsider its decision to not incorporate additional elements of value. Below we outline some of these additional elements of value and encourage ICER to stay up to date on the latest literature on all of the additional elements of value:

- **Productivity & Caregiver Burden** capture indirect costs to both patients and caregivers related to an illness. While challenging to capture in all situations, there are multiple methods to estimate loss of productivity.^{33,34} Similarly, lost productivity costs from illness can also be estimated for caregivers as well as the patients.^{35,36} In some assessments, ICER does consider productivity losses as part of a scenario analysis³⁷ but we believe this should be a consistent part of the base case to better capture the full value an intervention provides. From a societal perspective, productivity and caregiver burden are important factors in healthcare decision-making in order to better address the burden of disease.
- **Real Option Value** captures the beneficial aspects of when life-extending treatments allow patients to survive until future interventions are developed to better treat their condition. This additional value element has been estimated in economic models for antiretrovirals and oncology treatments.^{38,39,40,41,42}
- **Value of hope** incorporates the patient's perspective on survival gains, which is a concept that is not adequately accounted for in the current and proposed ICER framework. As a study published in Health Affairs indicates patients place significant value in survival improvements in the tail of the distribution above and beyond treatments that improve median survival.⁴³ Patients surveyed were asked to compare two treatment regimens for melanoma that, statistically speaking, yielded equivalent survival gains. A large majority of cancer patients chose the regimen that offered a 50% chance of twice the survival gain over a regimen that provided assurances of a shorter survival gain. Although the "sure bet" regimen provides assurance of a shorter survival gain, and "hopeful gamble" offers a 50% chance of twice the survival gain, a large majority of cancer patients chose the latter. This value of hope cannot be ignored. In recognition of the importance of long term survival, the American Society of Clinical Oncology (ASCO) explicitly incorporates survival improvements in its revised value framework through tail of the survival curve bonus points.⁴⁴

Incorporate innovative modeling approaches

BMS applauds ICER for proposing cure proportion modelling as its reference case when assessing "single or short-term transformative therapies (SSTs)."⁴⁵ We urge similar incorporation of innovative modeling approaches in the overall value framework. Methodologies for data extrapolation continue to develop and evolve, and BMS strongly recommends that ICER frequently review this literature, and incorporate the most rigorous and appropriate methodologies in an objective manner.



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Provide full transparency of economic models to all stakeholders

BMS is disappointed to see that ICER has chosen not to make economic models fully transparent to all stakeholders. While the limited model sharing program for manufacturers is a step in the right direction, it does not go far enough and will make it challenging to reproduce much less understand the model's structure & underlying assumptions. We also believe the process would benefit from peer-review of the model before it is finalized and applied in a review. For example, in the recent RA condition update focused on JAK inhibitors the draft report was not peer reviewed and ICER citing a need to rethink its model had to withdraw the document soon after release.⁴⁶ Although ICER has submitted components of its reviews to peer-reviewed journals after release of the final report—such as publications on the treatment for familial hypercholesterolemia and the hepatitis C virus^{47,48}—it has not published in peer-reviewed journals the complete evidence-based reviews of its topics.

New economic review section on ‘Controversies & Uncertainties’

Provide Ranges. BMS supports ICER's plans to expand discussion around the uncertainty and limitations of the work that it does. Though BMS believes that “expanded discussion” is a step in the right direction, we are strongly recommending that ICER address the uncertainty directly by providing ranges of all output estimates rather than the single point estimates that it often portrays in its materials. BMS believes in rigorous and transparent scientific processes, including communication and dissemination, and thus recommends that ICER not only address uncertainty in a direct (ie. quantitatively) manner consistently and throughout its “Evidence Reports”, but also upfront and transparently in its “Report-at-a-Glance” and any other communications it generates.

Underscore Uncertainty. Moreover, we recommend that ICER explicitly state that its results and conclusions are preliminary in nature, due to ICER's decision to rush to assess new treatments. As a result of this haste, ICER is often unable to include real-world, non-trial data collected from post-market studies, patient registries, and electronic health records (EHR), which are helpful in mitigating uncertainty. These data are often only available well after product launch, and thus provisions should be made by ICER to periodically revisit their assessments to include these data.

Incorporate more real-world evidence (RWE)

BMS recommends ICER aim to include more RWE in its assessments. This evidence base can be incredibly informative and complementary to clinical trial findings, especially when dealing with small population sizes. For multiple stakeholders these data may inform a greater understanding of a medicine's real-world effectiveness, safety and cost. As interest in RWE continues to grow, the research methodologies and databases have become more sophisticated. Overall, BMS participates in numerous pharmacoeconomic conversations and produces globally hundreds of publications per year.⁴⁹ For example, to better treat patients with rheumatoid arthritis (RA), BMS has published studies using real-world data from the Corrona, LLC RA registry to identify patient response to Orencia[®] based on key biomarkers.⁵⁰ Additionally, BMS has launched the ACROPOLIS (Apixaban ExperienCe Through Real-World Population Studies) program designed to generate evidence from clinical practice settings to help improve healthcare decisions in the prevention of stroke and embolism.⁵¹



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Implement a more transparent & consistent condition update process

With respect to condition updates, ICER has begun to conduct a few of these on an ad hoc basis but needs to be more transparent about changes in scope and what type of evidence will be considered. ICER proposes to formalize this update process and we encourage a more inclusive process as new data and science emerges. A more predictable approach to validate and adjust findings can be achieved by regularly retrospectively re-assessing the accuracy and relevance of value assessments against new and/or real-world data.

Avoid inappropriate cross country comparisons

ICER states there is a growing international use of its assessments and proposes to identify in each report how their evidence rating would crosswalk to the rating system Germany's HTA agency uses to describe a treatment's added clinical benefit. Substantial variations and important distinctions exist between these evidence rating systems that make this attempt to translate between them ill-advised and misleading. First, the evidence base of the assessment and analysis methodology may differ substantially, especially when it comes to the use of real world evidence. For example, ICER aims to include some real world evidence (RWE) while the Gemeinsamer Bundesausschuss (G-BA) aims to include RWE only in cases where a randomized clinical trial (RCT) is not possible. Second, the types of therapeutic effects considered patient relevant may differ depending on the therapeutic area and local clinical context. With respect to surrogate endpoints and biomarkers, these are considered on a case-by-case basis and will vary. Furthermore, the evidence evaluations occur in the local clinical context and there is variety between standards of care in the US and Germany. Lastly, even within Germany there is a variation between the benefit assessments across G-BA and the Institute for Quality and Efficiency in Health Care (IQWiG).^{52,53} Altogether this wide degree of variability would introduce a significant amount of uncertainty into attempting to crosswalk the evidence ratings. Based on these foundational differences between the rating systems and healthcare systems, we believe the proposal to crosswalk is a slippery slope towards inappropriate cross country comparisons. To avoid misuse we recommend ICER state in every assessment that "The results and conclusions of this report reflect assumptions based on US costs and the US healthcare system structure. As such, the results and conclusions presented herein do not apply to countries other than the United States."

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 treatments in isolation utilizing traditional cost-effectiveness analysis is wholly



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insufficient. Along with principles developed by the Healthcare Leadership Council,⁵⁴ 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;
- 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 value framework and processes.

Sincerely,

Mitch K. Higashi, PhD

Head of US Medical Health Economics and

Outcomes Research



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CANCER LEADERSHIP COUNCIL

A PATIENT-CENTERED FORUM OF NATIONAL ADVOCACY ORGANIZATIONS
ADDRESSING PUBLIC POLICY ISSUES IN CANCER

October 18, 2019

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

Dear Dr. Pearson:

The undersigned cancer organizations, representing people with cancer, health care professionals engaged in cancer care, and cancer researchers, are pleased to have the opportunity to comment on the 2020 update to the Institute for Clinical and Economic Review (ICER) Value Framework.

The undersigned organizations work to protect cancer patient access to quality care and to improve the treatments available to Americans diagnosed with cancer.

Ensuring a Patient Voice in ICER Reviews

The 2020 Value Framework update includes some patient-focused provisions that are described as an effort to strengthen the input from patients and patient groups. We have recommendations for changes to some of those provisions to ensure meaningful patient input.

- Engagement of patient groups in the development of the scoping document for reviews. ICER has indicated in the draft 2020 value framework that it will seek the advice of patient groups in the development of the scoping documents that guide reviews. We urge that this be done in all cases and that ICER engage patient groups with appropriate expertise on the disease or diseases that are the targets of the therapy being reviewed. Patients can advise about the burden of the disease, the benefits of current treatment options, and the unmet treatment needs for patients with the disease. In some cases, they will be able to share data about the reported quality of life of those with the disease and receiving current treatments. This information will ensure that ICER scoping documents more accurately represent the concerns and needs of patients.
- Include patients and disease experts as council members. The 2020 value framework does not provide for inclusion of those affected by the disease –

individual patients or practicing clinicians – as voting council members. The framework clarifies that it might on occasion happen that a council member will have expertise on the condition under review, if he or she does not have a disqualifying conflict. We urge ICER to reconsider this position and instead to include experts in the condition under review as voting council members. Such experts can provide valuable disease insights and information, just as they can during the scoping process. We anticipate that only those patients or clinicians without disqualifying conflicts would be permitted to serve as council members, but there should be no obstacle to identifying such individuals.

- Ensure adequate time periods for patient input on scoping documents and public comment on draft documents. The draft value framework recommended extending the public comment period for draft reports by one week. We recommend a longer extension. The patient groups that will be engaged in comment on draft reports are, by and large, understaffed and struggling every day to meet the needs of the patients they represent. These organizations simply need more time to review and respond to draft reports, including the time to consult with patients who may have received the technology under review, be eligible to receive the drug, or live with the disease targeted by the therapy and have important experience to share.

We have misgivings about the proposal to create a new “Patient Perspectives” chapter for ICER reports that will describe the input from patients, families, and patient organizations, as well as patient-generated evidence. While we will be pleased to see this information included in ICER reports, we fear that the decision to create a separate “Patient Perspectives” section means by definition that these perspectives will not be reflected in the core portion of the reports drafted by ICER. Instead, the patient-focused information will be available essentially for separate consideration rather than as an integral part of reports. Despite these reservations, we will participate in ICER reviews to ensure that the “Patient Perspectives” part of reviews is strong, detailed, and reflective of patient needs and experience.

The Importance of and Challenges Associated with Real World Data

In the draft value framework, ICER explains that it “has used and commits to continue using RWE provided the data are considered to be fit for purpose and of high quality, as judged by ICER’s evidence review team.” ICER also notes that, because it will be completing its evaluations of technologies before they have been launched in the market, high quality RWE may not in fact exist.

With these statements, ICER is signaling that its use of RWE will likely be limited and inconsistent.

Although we understand the rationale for completion of reviews of technologies before market entry, we have misgivings about this schedule because RWE is limited if it exists at all at the time of review. As a result, reviews do not reflect the benefits and risks of technologies that may be discovered only with use in clinical practice. We think that a different timeline for completion of reviews would result in reviews that reflect more accurately the benefits of new technologies, as confirmed by clinical trial data and RWE collected through clinical practice. More data about the quality of life of those being treated with the new technology are of special interest to us because of the potential of those data to bring an important patient perspective to the review.

Even within the time limits that ICER has established, patient groups will seek to provide whatever RWE that we can. However, we think that the ICER commitment to use RWE means that ICER should commit to obtain, evaluate, **and** use RWE. Under the terms of the value framework and in light of the schedule for review that ICER is generally following, we doubt that RWE will be utilized as it should be.

Addition of a “Controversies and Uncertainties” Section to Reviews

We have significant misgivings about the reliance on measures of quality adjusted life year (QALY) to capture all of the benefits of cancer treatments. For example, we are concerned that not all aspects of quality of life of cancer patients are captured by the patient-reported outcome (PRO) measures that are currently utilized and reflected in QALYs. We are not alone in our concerns about QALYs; there is a strong history of caution about their utilization in the United States.

We understand from the value framework revision that ICER is fully committed to the use of the QALY in its reviews. We are pleased that ICER, in response to stakeholder comment on the framework, has proposed a “Controversies and Uncertainties” subsection of its reports that will allow for exploration of different model variations. In the value framework revision, ICER writes, “Although the current layout of ICER reports includes information on these issues, we feel it will be helpful to consolidate and expand discussion of factors related to uncertainty, including lack of information on natural history, limitation of the data on patient outcomes, difficulties translating existing data into measures of quality of life, and disagreements over the plausibility of certain inputs or assumptions.”

Although the Controversies and Uncertainties section fails to answer many of our misgivings about the singular reliance on QALY measures, we will seek to make this section of reports on cancer technologies meaningful by active participation in the ICER process, identifying areas of uncertainty and lack of data and providing RWE and other data about patient quality of life that are available to us.

We appreciate the opportunity to comment on the revised value framework, to be used beginning with reviews in 2020. We urge your careful consideration of our concerns and recommendations, which will move the review process toward a more patient-centered one.

Sincerely,

Cancer Leadership Council

Cancer Support Community
Children's Cancer Cause
Fight Colorectal Cancer
International Myeloma Foundation
Lymphoma Research Foundation
National Coalition for Cancer Survivorship
Ovarian Cancer Research Alliance
Prevent Cancer Foundation
Susan G. Komen



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October 18, 2019

Steven D. Pearson, MD
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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.

Patient Engagement

In section 1.1 of the ICER revised framework, ICER states that evidence assessment is “one component of ICER’s broader effort to provide mechanisms through which all stakeholders and the general public can engage in discussions on how best to use evidence as the foundation for a more effective and sustainable health care system.” We align with ICER on this point and support efforts to incorporate patients into discussions regarding a more effective and sustainable health care system.

On page 3, lines 360-365, ICER states:

Even with its population-level focus, however, the ICER value framework seeks to encompass and reflect the experiences and values of patients. Representing the diversity of patient outcomes and values in a population-level framework is difficult because there will always be an inherent tension between average findings in clinical studies and the uniqueness of every patient. There will also always be diversity in the way that patients view the balance of risks and benefits of different treatment options.

We appreciate ICER’s acknowledgement of this dichotomy between value assessment and patient values, needs, and preferences. We volunteer to work with ICER to be world-leaders in finding ways to better incorporate the patient voice into value assessments.

We also appreciate ICER’s update to the framework to debrief with patient groups after a report is complete. We look forward to better understanding the formal debriefing process and volunteer as a resource to help ICER finalize that process.

It is also important for ICER to recognize the challenges facing patients and patient advocates as they seek to engage in ICER’s processes. Access to the evidence is a critical component of engagement. However, stakeholders who are not affiliated with an academic institution or who do not have the means to access academic databases or purchase expensive journal subscriptions are many times unable to review the data necessary to participate in the value assessment process. While we recognize that the limitations posed by the publishing system are not due to actions by ICER, we are seeking solutions to this barrier.

Real World Evidence

On page 4, section 3.1, ICER “reaffirms use of existing real-world evidence.” We appreciate this commitment and encourage ICER to work with patient advocates to clearly outline the types of real-world evidence that will be accepted for use during value assessments. We agree with ICER’s statement on page 5, lines 409-411 that “...randomized controlled clinical trials have

their own limitations and are often inadequate to address all questions relevant to assessments of comparative clinical effectiveness.” We also agree with ICER in that patient-reported outcome studies can provide evidence not always captured in clinical trials. As noted above, CSC has a Cancer Experience Registry of over 14,000 participants and we would like to work with ICER to leverage the data from the Registry and determine how such sources can be meaningfully integrated into ICER’s value assessments. In addition to Registry findings, our team of 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. We believe that patient level data must be incorporated. If this level of data is not readily available, it IS ICER’s responsibility to secure it in order to be fully informed.

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.

Cost per Quality-Adjusted-Life-Year and Equal Value of Life Years Gained

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 recognize the limitations of the QALY and work towards inclusion of a more patient-centered measure. 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, we agree with Weinstein, Torrance, and McGuire (2009) when they stated 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.

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.

The Belmont Report also emphasizes the importance of including patient experience data in the research process. In its discussion of basic ethical principles for research involving human subjects, the Belmont Report identifies beneficence as an obligation for both individual investigators and society at large to: (1) do no harm and (2) maximize possible benefits and minimize possible harms. With regard to particular projects, the Belmont Report states “investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation.” Similarly, in the case of scientific research in general, the Belmont Report provides “members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.” It is essential that ICER both increase opportunities for patients to submit valuable data and require patient data be incorporated in its efforts to better define value, whereas beneficence is an obligation, not merely “other benefits or disadvantages” and/or “contextual considerations.”

Additional Dimensions of Value

ICER states on page 13, lines 608-610 that methods for the quantification of value dimensions highlighted by Lakdawalla et al. (2018) are “viewed by many health economists as too exploratory for routine incorporation into assessments.” The “value of hope” is given as one example. As noted in CSC’s letter to ICER regarding the proposed Value Assessment Methods for “Single or Short-Term Transformative Therapies,” ICER states that they “believe there are significant risks or double counting within the QALY or within existing “other benefits” or “contextual considerations” that ICER already includes as part of its value framework.” ICER also notes that such additional elements of value are all “unidirectional” and would all “add” to treatments, and none have negative scores that would help balance out added value within an opportunity cost framework for determining the cost-effectiveness threshold.” Finally, it is noted that methods for measuring additional elements of value are “not mature” and “further research is needed before it can be determined how to measure them.” As a result, ICER proposes that “no quantitative integration of additional elements of value” will be included in the value assessments framework for the assessment of SSTs. However, patient input will be sought regarding the “value of choice among treatments with a different balance and timing of risks and benefits.” We do not believe that the stated “value of choice” appropriately captures the concept of the “value of hope.” We disagree that the concept of the value of having the choice among treatments with different balance and timing of risks and benefits captures the same concepts as the value of hope. We are currently validating a new tool called the “Valued Outcomes in the Cancer Experience” or the VOICE measure. This project began as a study of what patients hope for and has evolved into a measure of their values and how much control they believe they have over what they consider most valuable. We believe that this measure could be useful to ICER and propose a meeting to discuss potential collaboration on this topic.

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.
- Incorporate real world evidence whenever possible and partner with patients, patient advocates, and other experts to ensure the inclusion of such evidence from registries, qualitative analyses, patient studies, etc.
- 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 (which is inclusive of patient experience data) are available.
- Recognize the limitations of the QALY and evLYG and incorporate alternative measures such as multi-criteria decision analysis.
- Ensure that “other benefits or disadvantages” and “contextual considerations” play a key role in assessments with a specific focus on patient experience data. 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 within two months of new evidence becoming 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 and voting) 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 voting.

- Allow for weights to be assigned based on user preferences and assign higher levels of value to components that are most important to patients.
- Partner with patient advocates to create and disseminate information necessary to understand and participate in the value assessment process.
- 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. Engage in additional data collection if data doesn't exist.
- Include costs that are representative of the price most relevant to the patient.
- Change ICER comment period to 90 days to allow for sufficient time for patient and patient advocate feedback.

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, MSW
Executive Director, Cancer Policy Institute
Cancer Support Community Headquarters

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October 18, 2019

Institute for Clinical and Economic Review
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Dear ICER Review Panel:

Genentech appreciates the opportunity to provide input on ICER's 2020 Value Framework. As a leading biotechnology company, Genentech discovers, develops, and manufactures novel medicines to treat patients with serious and life-threatening conditions. We support the goal of policymakers to lower health system and patient out-of-pocket costs. To achieve this optimally, stakeholders must work together to find sustainable, system-wide solutions that lower costs while protecting scientific innovation and access to breakthrough treatments.

ICER is one of several independent, health technology assessment (HTA) organizations that seek to assess the value of drug treatments in the U.S. The impact of such a role is broad, far-reaching, and cannot be achieved alone. We believe success is only possible with a process that sufficiently engages all relevant stakeholders, is transparent, and based on a foundation of rigorous science and methods.

To date, Genentech has been an active participant in fifteen value framework topics that range from product-specific reviews to broad health policy topics. We provide comments based on our deep experience and with the ultimate intent to optimize health care in the U.S. Our input on the 2020 Value Assessment Framework specifically focuses on three categories to enhance the credibility, validity, and representativeness of ICER's current approach:

1. **Evidence.** Insufficient use of real-world evidence (RWE) and discussion of uncertainty in ICER's framework does not align with real-world decision making.
2. **Methods.** ICER further entrenches the reliance on cost-effectiveness analyses (CEA) as the primary mechanism to align value and price. Development of new value assessment methods intended to better reflect patient, societal, and disease-specific considerations is necessary to facilitate their acceptance and utilization.
3. **Process.** Insufficient transparency, patient involvement, and monitoring the real-world impact of their work limits the validity and credibility of ICER's approach.

Evidence

1. Insufficient use of RWE and discussion of uncertainty in ICER's framework does not align with real-world decision making.

ICER's incorporation of RWE remains insufficient and is misaligned with how health care decision makers evaluate value. Although there are limitations associated with RWE, clinicians, payers, and health authorities recognize the need for evidence that goes beyond clinical trial data.¹⁻⁶ They use RWE not just to assess treatment safety but to better understand the effectiveness of interventions when making treatment, coverage, and regulatory decisions. ICER can better leverage RWE to inform the level of certainty in their Evidence Rating Matrix, validate results from the cost-effectiveness model, and generate additional scenario analyses to inform decision making.

1.1. Summarizing and critically evaluating RWE is essential to address the evidence needs of health care decision makers.

ICER can improve the use of RWE in reports by appraising studies in accordance with best practices and summarizing them in a new subsection within the "Comparative Clinical Effectiveness" chapter.⁵⁻¹⁰ Rather than using arbitrary criteria (e.g., N>1,000 patients), RWE should be critically and independently evaluated to better align with the evidence needs of decision makers. 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. This approach provides health care decision makers with the full body of evidence to inform their decisions while allowing ICER to appraise the quality of the evidence.

1.2. Incorporating clinical outcomes from real-world studies into ICER's Evidence Rating Matrix will ensure that the determination of comparative clinical effectiveness reflects all available evidence.

RWE can demonstrate benefits that extend beyond trial settings and should inform an intervention's Evidence Rating. By formally appraising the quality of real-world studies in accordance with best practices, ICER can inform decision makers about the limitations associated with RWE and account for those limitations through the level of certainty in the evidence.⁵⁻¹⁰ This approach allows for a more precise judgment of net health benefit that reflects the totality of available evidence. For example, the incorporation of RWE demonstrating a substantial net health benefit when only a small benefit was observed in clinical trials could be reflected as a change from a "B" to a "B+" rating for the intervention.

1.3. Real-world clinical and economic outcomes are important to highlight potential variability in long-term cost-effectiveness and validate ICER’s CEA.

Health care decision makers should have a range of information that enables them to make informed judgments. Scenario analyses informed by real-world clinical outcomes provide further insight into the cost-effectiveness of interventions in real-world populations and should be discussed in the new “Controversies and Uncertainties” sub-section. For example, incorporating recent RWE for Xolair® (omalizumab) into a cost-effectiveness model resulted in a lower cost per quality-adjusted life year (QALY) than calculated in ICER’s model which relied solely on data from clinical trials (Table 1).^{11, 12} Without a scenario analysis that incorporates this RWE, the implications of the holistic evidence base are lost.

Economic outcomes from real-world studies can also validate CEA results and provide additional perspectives about the economic value of interventions that may not be captured by a traditional CEA (e.g. economic benefits of cumulative life-years saved to the U.S. health care system).¹³ While not all interventions may have real-world or economic outcomes, it should be included and discussed in this section, when available, to corroborate or counter the findings of the model. By doing so, ICER can improve confidence in the model results or provide decision makers with the range of outcomes to inform their decisions.

Table 1: Cost per QALY of Xolair compared to Standard of Care*

	Clinical Input	Year of Cost reported	ICER
ICER 2018 Asthma Review ¹¹	Efficacy-based	2018 (US Dollars)	\$325,000/QALY
Sullivan et al, 2019 ¹²	Effectiveness-based	2018 (US Dollars)	\$75,319/QALY

*Standard of care was defined as inhaled corticosteroids and at least one additional controller agent
Abbreviations: QALY=quality-adjusted life year

1.4. Cross-referencing ICER’s Evidence Ratings to German Evidence Ratings risks misinforming decision makers.

ICER should not translate their Evidence Ratings into German Evidence Ratings. These rating systems were not developed with the intent to inform or be translated to one another. They employ different methodologies, rely on different evidence, and are utilized for different purposes.¹⁴ Cross-referencing the Evidence Rating categories may cause decision makers to undervalue interventions and misinterpret their potential benefit. For example, an intervention categorized as “C+” would be determined to have “no added benefit” when translated to the respective German Evidence Rating category. However, ICER determined that there is moderate certainty that these interventions may provide a comparable or small net benefit. As

a result, it is not that these interventions do not provide added benefit, but rather that the evidence may not yet be mature to determine the benefit with certainty. ICER's current Evidence Rating matrix and the proposed updates allow for a more precise evaluation of the net health benefit of an intervention. Cross-referencing the categories would dilute these efforts and mischaracterize the value of interventions.

Methods

2. Development of new value assessment methods intended to better reflect patient, societal, and disease-specific considerations is necessary to facilitate their acceptance and utilization.

As a self-appointed organization that seeks to use their value assessment framework to *"translate this evidence into policy decisions that lead to a more effective, efficient, and just healthcare system"* ICER has a responsibility to:

- Enhance their self-established framework by continually refining and improving it, particularly in the areas of limitation they themselves acknowledge
- Engage in a transparent manner with the community of stakeholders who are actively trying to innovate methods in value assessment
- Make clear strides to move beyond traditional value assessment approaches instead of further entrenching their use

2.1. ICER's proposed approach does not adequately reflect patient and societal preferences, limiting the relevance and utility of their reports.

Traditional value assessment methodologies and metrics were not designed for our increasingly complex health care landscape. Innovation is necessary to ensure the relevance and utility of ICER's reports.

While we recognize methodological challenges exist in the quantification of additional measures of value, by discussing these components separately, and qualitatively, the current process does not capture the holistic value of treatments. ICER has previously stated *"...the methods for quantifying these dimensions of value remain exploratory and lack any consensus among academic health economists. That by itself would be a strong argument not to consider attempting to quantify them as part of the assessment of SSTs [single or short-term transformative therapies]."*¹⁵ However, it is for precisely this reason we believe ICER should, in partnership with academia and policy makers, seek opportunities to further develop these methodologies to increase their validity, acceptability, and application in value assessments.

ICER has indicated they will explore collaborations with organizations to generate RWE to complement published literature sources in reviews. While ICER needs to provide more transparency around which organizations and the types of data they intend to generate, we commend the willingness to partner with third party experts. Similarly, we encourage ICER to explore collaborations with research groups working to advance methods for alternative measures of value to identify solutions to the previously stated methodological challenges. For example, as per the National Pharmaceutical Council's (NPC) recommendation in the open input period, ICER could consider partnering *"with researchers such as Chuck Phelps and 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."*¹⁶ Doing so will ensure reports provide a more holistic and cohesive summary of value that reflects the appropriate relative importance of additional measure of value, comparative effectiveness, and long-term cost-effectiveness for health care decision making.

2.2. A single threshold range for all therapies overlooks important contextual considerations, particularly for rare diseases.

ICER has the opportunity to have a positive impact on the U.S. health care system by providing objective data to facilitate informed decision making by key health care stakeholders. However, with this, ICER has a responsibility to take great caution with their methodologies to ensure patients' access to necessary treatment remains at the forefront of their guidance. ICER should therefore acknowledge the uniqueness of appraising value in rare diseases by reinstating different thresholds and measures of value for rare and non-rare diseases.

The importance of context in value assessment is highlighted by the NPC's Guiding Practices for Patient-Centered Value Assessment which states *"no single threshold can or should be universally applicable; thresholds are likely to vary by population and disease."*¹⁷ While we recognize the equity concerns of applying differential thresholds for different disease types, the importance of recognizing the unique challenges faced by patients with rare diseases is well established. In addition to the substantial burden associated with rare diseases due to differing clinical needs relative to patients with more common conditions, patients often face delays in diagnosis and support due to the limited awareness and understanding of their conditions, and the lack of rare disease specialists.¹⁸ ICER should undertake research with key stakeholders to identify an appropriate willingness-to-pay threshold or other value attributes for patients with both rare and non-rare conditions to ensure relevance to today's U.S. population.

ICER states in their 2020 proposal “...today it no longer seems necessary to make important exceptions to applying standard cost-effectiveness thresholds to analyzing the value of treatments of rare or ultra rare conditions” to help sustain innovation, as was historically the case.¹⁴ However, with 95% of rare diseases lacking an FDA approved treatment there clearly remains a substantial need for continued innovation to address the high burden and unmet need experienced by patients with these conditions.¹⁹

2.3 The use of evLYG to supplement the QALY is methodologically flawed and does not address the limitations of CEA at capturing holistic value

ICER’s proposal to use Equal Value of Life Years Gained (evLYG) to supplement the QALY does not support a more holistic view of value. By excluding utility, not only does evLYG propagate the same underlying limitations of cost-effectiveness and cost-utility analysis but it overlooks important contextual considerations. If ICER wishes to use this metric, we recommend:

- evLYG should be used as an additional outcome only for diseases where treatment offers survival benefit.
- An incremental cost effectiveness ratio should not be calculated for evLYG, given no established threshold value exists in the literature. If ICER wishes to use one, research needs to be conducted to identify an empirically justified one.

The evLYG metric is inherently flawed because not all treatments are life extending nor are all diseases fatal. Health is about more than just survival, and evLYG’s failure to capture health improvements, such as increased physical functioning or reduced chronic pain, makes it challenging to compare outcomes for interventions for chronic conditions with those for fatal conditions. Additionally, when quantified in the context of a CEA, they have an inherent bias against conditions that are largely non-fatal.

To better reflect real-world decision-making processes, which leverage the totality of the available evidence, ICER should also continue to include additional economic endpoints to address outcomes that are important to decision makers (e.g. use of cost per remission in recent rheumatoid arthritis report).²⁰ By adopting this approach, not only will ICER’s approach align with real-world decision making, but it could substantially enhance the utility and relevance of the reports, particularly for large class reviews.

Process

3. Insufficient transparency, patient involvement, and monitoring the real-world impact of their work limits the validity and credibility of ICER's approach.

We appreciate the concerted efforts by ICER to improve the process by which they conduct their value framework assessments. Given our extensive involvement in several ICER reviews, we believe key areas in the process can continue to be improved.

3.1. By not providing fully executable and replicable economic models, ICER is significantly undermining their credibility.

We reiterate our prior feedback that economic models released as part of ICER's transparency initiatives should be fully executable. In our experience with the draft cost-effectiveness models, none of the inputs could be altered or tested. This significantly undermines ICER's credibility, and limits the ability to sufficiently review the model and provide meaningful feedback.

The joint ISPOR-SMDM task force on modeling good research practices cites transparency and validation as two critical mechanisms to successfully achieve the acceptance of health economic models.²¹ The benefits of this include the ability to conduct cross-validation which ultimately establishes trust and confidence in the model. All model-based activities are subject to imperfect information and judgements in the context of uncertainty. While we appreciate the challenges with protecting intellectual property of the models, ICER should follow the example of other HTA agencies and prioritize sharing executable models.

3.2. Preliminary model presentations using incomplete models undermines ICER's commitments made during the engagement process.

ICER should improve the transparency of the modeling process by reviewing complete models during the preliminary model presentations to manufacturers. In our recent experience with ICER's asthma and rheumatoid arthritis reviews, the cost-effectiveness model and selection of model assumptions were incomplete. This results in manufacturers only reviewing the model once it becomes public - countering the fundamental purpose of reviewing preliminary results in advance of draft report publication. ICER should honor the commitments made during the engagement process and afford the opportunity to respond prior to public dissemination of their work.

3.3. Clarity of reassessment criteria and allowing adequate time for new evidence generation are essential for an effective reassessment process.

We support the reassessment of ICER's reports based on the availability of new evidence. Reassessments, including revisions to previous Evidence Ratings to match the new proposed ratings, should reflect the best available evidence to inform health care decision making. This process can be further optimized by:

- 1. Tailoring the assessment time point to the evidence, endpoints, and decision maker needs.** One year may not be a sufficient amount of time for new evidence to be generated. Outcomes of interest to decision makers may require a longer follow-up period to mature, and there is a lag between product approval and when there is sufficient real-world use for analyses. For example, the Final Evidence Report assessing PCSK9 inhibitors was published in 2015; however, new evidence was not available until 2017 for evolocumab and 2019 for alirocumab.²²⁻²⁴
- 2. Defining explicit and transparent evidence criteria that will trigger reassessment.** We encourage ICER to align the criteria for reassessment with how decision makers evaluate evidence. RWE and health economic evidence inform formulary, coverage, and policy decisions, and should be considered when reevaluating the results of a report. Defining the criteria for reassessment would encourage additional research to address evidence gaps.
- 3. Applying new Evidence Rating categories only to future reports and updates.** ICER should not apply new Evidence Ratings to previous reports without accounting for new evidence. Revising previous ratings without accounting for new evidence may misinform decision makers and mischaracterize the value of an intervention.

3.4. Deeper engagement with patient communities and emphasis of the “Patient Perspectives” chapter in ICER materials will ensure the patient voice is adequately expressed.

The “Patient Perspectives” chapter is an appropriate step towards achieving the goal of incorporating patients into the assessment. To better achieve this, we recommend:

- The opportunity to co-author this chapter should be extended to patient organizations. It would be remiss to detail patients’ perspectives without their direct input.
- Evidence generated by patient advocacy groups, such as survey data, should be summarized in detail. Further, ICER can partner with these groups in generating such evidence.
- A systematic review of the literature, conducted by ICER, should be detailed in this chapter.
- The chapter should be presented as a stand-alone agenda item in the public meeting and highlighted in the “Executive Summary and “Report-at-a-Glance.”

3.5. Formal appraisal of the impact, quality, and validity of ICER's evaluations is essential to understand their intended and unintended consequences.

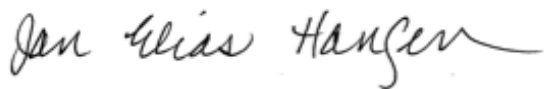
As the primary authors, it is ICER's responsibility to understand the intended and unintended consequences of their evaluations. Since 2014, ICER has generated 27 assessments that are intended to inform evidence-based decision making in the health care system. As proprietors of these reports, ICER should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

Conclusion

In conclusion, we commend ICER for continually refining their value assessment framework and encourage further refinement by leveraging all available evidence and patient-centric, innovative methodologies. However, to achieve the goal of supporting a more effective and efficient health care system, ICER must prioritize topics that will reduce or eliminate low value care and expand their assessments beyond pharmaceutical products to other health technologies (e.g. procedures, diagnostics, devices, etc). By adopting this broader approach, ICER will ensure their evaluations inform meaningful change across the entirety of the health care system.

As an organization that shares ICER's goal around 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 written in a cursive, flowing style.

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

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October 18, 2019

SUBMITTED VIA EMAIL

Steven Pearson, MD
President, Institute for Clinical and Economic Review
Boston, MA 02109 USA
Email: publiccomments@icer-review.org

RE: ICER 2020 Value Assessment Framework

Dear Dr. Pearson,

On behalf of the [Global Healthy Living Foundation](http://www.ghlf.org) (GHLF) and the arthritis patient community CreakyJoints, we thank ICER for providing us with the opportunity to provide comments and input as you reflect upon and consider refinement and changes to the revised value assessment framework for 2020. By way of background, GHLF is a 20-year-old non-profit patient organization reaching millions of chronically ill patients and their caregivers across the country through social media, community events, and online support and education. Our ArthritisPower registry of more than 22,000 patient participants was developed as part of the National Patient-Centered Clinical Research Network (PCORnet) with data capture mapped to the PCORnet Common Data Model. GHLF works to improve the quality of life for patients living with chronic disease by making sure their voices are heard and advocating for improved access to care at the local and federal level. Our patients live with chronic conditions including arthritis, psoriasis, gastrointestinal disease, cardiovascular disease, and migraine.

We encourage and applaud your stated commitment to continually evolve and improve the ICER framework by engaging with patient organizations like ours, in order to develop more transparent, robust and objective models and methods as you develop and define the 2020 Value Assessment Framework. However, we continue to emphasize the danger of ICER's approach on defining and determining the value of treatment and clinical efficacy without incorporating a multi-stakeholder perspective since this necessarily precludes the development of a multi-model approach that considers multiple stakeholder perspectives.

Multi-stakeholder input is essential for the development of the Value Assessment Framework in order to ensure it remains objective and does not unfairly favor any one stakeholder group. As asserted by us previously, and on numerous occasions, the patient perspective remains of paramount importance and we are hopeful that ICER becomes an advocate for the inclusion of real-world data (RWD) and real-world evidence (RWE) in light of ICER's agreement and acknowledgement of the limitations that surround only the use of clinical trial data. Clinical trials data fails to reflect real-world experience and among other shortcomings, and by its very nature, and design, tends to focus on more short-term outcomes as opposed to the longer-term experience that patients have when living with a chronic disease. In addition, the experience of patients living with a chronic disease may not be consistent over a lifetime. There are interruptions and periods of flares, remission and varying disease activity. This waxing and waning remain

a hallmark of living with many chronic diseases which must be accounted for and cannot be addressed by assuming, as the QALY does, that there exists a measure of “perfect health”.

If it is ICER’s commitment to ensure that patients have improved quality of care and hence are able to access treatments, we caution against the use of Quality Adjusted Life Years (QALY) alone. As previously stated by us in our earlier comments to ICER, QALYs do not adequately reflect the real-world patient experience and remain controversial among many experts. Among other things, the QALY ignores ethical societal concerns and puts patients at peril by reducing individuals to an average arbitrary number. The serious problems associated with the QALY measure is no longer a matter of debate among experts and academics. There is growing consensus that QALYs inherently do not sufficiently capture heterogeneity in patients based on age, disease severity and patient preferences. In addition, sub-group analysis is essential to account for heterogeneity of the patient experience, especially for chronically ill patients and we encourage inclusion of sub-group analysis.

Simply acknowledging the inherent challenges around the QALY while continuing allegiance to similar metrics sends a disturbing message. ICER’s solution to incorporate the Equal Value of Life Years Gained (evLYG) amounts to addressing one problem by substituting it with another. This is all the more reason for ICER to incorporate RWD and RWE into their model while simultaneously incorporating the patient and caregiver perspective throughout the process of deliberation and development.

The evLYG fails to account for individual patient experiences. For example, the evLYG is inadequate for patients with chronic disease conditions because it fails to take into account quality of life (QOL) and symptom improvement impacts which remains a central concern in managing any chronic disease. For patients with disabilities, the evLYG fails completely because it does not account for potential improvements in QOL as a measure when valuing treatments.

Finally, the credibility of any model or analyses lies in part on transparency and repeatability. We encourage ICER to provide complete transparency and access to their models. In order to develop a rigorous model, a multi-stakeholder invitation to critique remains integral. Through critique one might understand where biases lie, what scope there is for repeatability to assert validity and by doing so enhance the model to higher standards of objectivity. We encourage ICER to reveal the nuts and bolts of their models to the larger stakeholder community.

Thank you for the opportunity to comment on this proposed guidance.

Respectfully submitted,

A handwritten signature in black ink, reading "Shilpa Venkatachalam". The signature is fluid and cursive, with the first name "Shilpa" and last name "Venkatachalam" clearly distinguishable.

Shilpa Venkatachalam, PhD, MPH
Associate Director, Patient-Centered Research



October 18, 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: ICER 2020 Value Assessment Framework proposed changes

Dear Dr. Pearson:

On behalf of Gilead Sciences, we appreciate this opportunity to provide input into ICER's 2020 Value Assessment Framework Proposed Changes. We hope that ICER will take our recommendations into consideration so that we can usher in a better healthcare system for all patients.

Gilead Sciences is a research-based biopharmaceutical company that discovers, develops, and commercializes innovative medicines in areas of unmet medical need. Gilead's therapeutic areas of focus include HIV/AIDS, liver diseases, cancer, inflammatory and respiratory diseases. Our portfolio of more than 25 products contains a number of category firsts, including complete treatment regimens for HIV and chronic hepatitis C infection available in once-daily single pills and the first CAR T therapy approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.

Introduction

In the proposed changes to the 2020 Value Framework (VF), ICER has explored various modifications to its methodology and has recommended adaptations to enhance future value assessments. The challenge with the current proposed adaptations is that they do not go far enough towards ICER's goal to "assist patients, clinicians, life science companies, and other stakeholders gain a fuller understanding of the potential benefits and harms of health care innovations, as well as their long-term cost effectiveness and potential health-system budgetary impact."¹ ICER did not accept most of the points Gilead raised in the last comment period, that would have moved ICER's VF forward towards supporting greater applicability and relevance of assessments, namely the modification or addition of

the following: 1) Thresholds adjusted for inflation that are carefully and individually considered on a case-by-case basis and vary according to disease, prevalence, and stakeholder, including cure-specific thresholds. 2) Holistic capture of other elements of value outside of the QALY, acknowledging the weakness of this measure. 3) Discounting of benefits to balance the needs and health of the current generation with future generations. 4) Significant innovation in health technology assessment (HTA) to capture the substantial value of curative therapies. 5) Inclusion of benefits and costs relevant to caregivers, patients, and employers as well as economic outcomes in the base case. 6) Appropriate assessment methodologies to account for new treatments for diseases that have no alternatives. 7) A more robust approach to time horizons to allow for more informed policy decisions. 8) Accommodation in the timing of assessments for treatments approved with single-arm trials.

ICER appears to seek a move toward shifting the health policy conversation in the direction of value. The limitations in its current VF, however, will prevent it from being truly relevant to the social and political needs of the US, which is far more diverse than other markets that have single-payer health systems. For ICER to be successful, it needs to think much more innovatively in a variety of ways, such as:

- **Including a collaborative real-world evidence (RWE) approach that matters**
- **Setting the societal perspective as the base case**
- **Enforcing the grand bargain**

Below we more fully expand on each of these important issues.

1. ICER needs to commit to broadening its use of RWE to understand the costs that medicines offset and benefits they provide

There are additional steps ICER should adopt with RWE to more comprehensively capture the full gamut of treatment value. Randomized clinical trials (RCTs) cannot answer all the necessary questions for decision making, especially if the patient population assessed is not representative of those seen in clinical practice. Real world studies are especially important as they provide insight into various treatment aspects and patient outcomes.² To fully capture the effectiveness, safety, tolerability, cost-effectiveness, and patient impact a drug provides, RCTs must be supplemented with RWE in the base-case assessment. Gilead appreciates ICER's efforts to incorporate RWE into its assessment and its willingness to explore collaborations with organizations that could support RWE evidence generations in assessments. We would further recommend an enhanced inclusion of RWE to capture lifetime resource utilization in disease assessment, more accurate and real world evaluation of efficacy and incorporation of elements not traditionally captured in clinical trials, such as patient reported data and adherence.

ICER's recent assessment of Rheumatoid Arthritis (RA) shows the tremendous complexity of modelling a disease characterized by extensive heterogeneity that could be improved with the

incorporation of RWE. Complexities of this disease include differences in patient type and disease manifestation, multiple drug choices and harder to measure subjective patient outcomes (*e.g.*, pain, fatigue, activities of daily living), requiring extensive assumptions in the modelling of this disease.³ For example, adalimumab differed by nearly 1 QALY and \$433,420 in total payor costs in ICER's 2017 and initial 2019 RA assessments.^{4,5} Although extensive changes between each model contributed to this discrepancy, ICER also missed a significant opportunity to use RWE from electronic patient records to more comprehensively analyze RA. Greater use of RWE could negate the use of modelling at all in some cases. Drugs such as adalimumab that are reaching the end of their exclusivity have very significant evidence that sits within patient records enabling a more accurate assessment of healthcare resource utilization and outcome. It is well recognized that there are principal differences in patient characteristics between RCTs and RA registries,⁶ which offer the opportunity for ICER to perform more exact assessments and better capture the differences between real-world experience and experimental context.

Greater incorporation of RWE will enhance the modelling that is a component of ICER assessments of new treatments. RWE can better represent the lifetime costs for diseases that are excluded through study design in RCTs. For example, lifetime costs for infectious disease are a fundamental tenet of the demonstrated value of a treatment that prevents and reduces transmission. Improperly-designed model simulations, however, can significantly underestimate these costs. In HIV, for example, patients carry with them a burden of a lifetime of treatment costs, which are not captured in clinical trials. These lifetime costs can be quite substantial and underestimated in studies that model these costs. A recent study found that discounted life time costs for HIV patients between 25 and 69 in the US were \$850,000 higher than the unaffected population.⁷ In comparison, a prior study that simulated these costs through a model reported a discounted lifetime cost of nearly a third less.⁸ In this example, analysis of real data using health claims rather than simulations for deriving costs, combined with the incorporation of a longer time horizon and estimation of costs not tied to CD4 count, provided more accurate RWE-based measures of life-time costs. In addition, it is hard for models or RCTs to accurately capture the long-term co-morbidities from having increasingly common diseases related to behavioral health. For example, in patients suffering immune-mediated inflammatory diseases the incidence of depression, anxiety and other behavioral health conditions is higher than in the general population. While captured in RWE, these co-morbidities are not commonly captured in RCTs or ICER assessments.⁹ In another example of hepatitis C virus (HCV) infection, chronic liver disease may appear many years after initial infection and can put further burden on patients and healthcare systems¹⁰, but this is less likely to be reflected in the current modelling approach ICER applies. These are situations where RWE can reduce uncertainty and enhance understanding and more accurate characterization of the advancement of appropriate treatments to give patients over long periods of time.

ICER should collaborate with health technology companies and manufacturers to best capture sources of real-world data. In oncology, which is particularly characterized by a narrow patient population, RWE provides critical information that complements safety and efficacy found in RCTs, as cancer patients tend to be older and sicker than those in clinical trials.¹¹ RWE should also help

ICER towards a better definition of when a disease has been cured in patients, which can be accelerated with breakthrough therapies. While this varies across diseases, RWE can help demonstrate exactly where a patient falls into a health state or overall survival equivalent to that of the age- and sex-matched general population. For example, this has been demonstrated in DLBCL both for CAR T and other chemotherapies.^{12,13,14} Although CAR T therapies are often “covered,” delays in therapy caused by prior authorizations and other paperwork can be deadly for the patient who needs these life-saving treatments. For example, delays of only a month in the treatment of Acute Lymphocytic Leukemia patients has an associated loss of nearly 10% of their social value, or \$637 million.¹⁵ This requires better payment mechanisms and reform of payment policies to improve patient access to CAR T therapies.¹⁶ RWE is gaining traction as a respected source of information in pilot studies such as those spearheaded by Friends of Cancer Research, which involves collaboration with six organizations, including IQVIA. In addition, the FDA has previously accepted treatments in oncology on real world data (RWD) alone¹⁷ and has gone so far as publishing a framework for its RWE program.¹⁸ Sources of RWD are vast, providing excellent opportunities to measure costs, resource use and added benefit, ranging from electronic health records (EHRs), information from fitness and health tracking wearable devices, to meticulously recorded health information recorded by health technology companies. ICER should actively seek collaboration with these companies to best source their RWD. This is especially important in oncology, where sources of RWD do not offer sufficient variety nor volume to overcome issues of “spuriousness and overfitting”.¹⁹

ICER should expand the time period of an assessment to allow for the development of RWE, especially in areas where data are missing in patient-reported outcomes, disease natural history, safety and durability. An important consideration in ICER’s collaborations is to allow for assessments to span 12 months in areas where evidence is low but where this could be alleviated through the collection of RWE. This could include a better collection of quality of life data and QALY data or registry data mining that could shed light on key issues of adherence, durability, safety and greater understanding of the standard of care reflected in datasets that comprehensively measure natural disease history. ICER should notify manufacturers 12-24 months before launch of the likelihood of an assessment and the kind of RWE manufacturers will need to provide.

2. If ICER continues to oppose the societal view as base case, it will be irrelevant for policy considerations.

For wider acceptance and relevance, ICER will need to make significant revisions to the VF towards the capture of costs and outcomes that are important to patients. ICER should seek to create a VF and associated processes that command greater inclusivity for assessments for wider applicability and better informed decision making. ICER seeks a value framework that “*will form the backbone of rigorous, transparent evidence reports that within a broader mechanism of stakeholder and public engagement, will help the United States evolve toward a health care system that provides fair pricing, fair access and a sustainable platform for future innovation.*”²⁰ Yet ICER’s current base

case omits the costs to one of the most important stakeholders, the patient. Moreover, this perspective excludes the voice of employers, patient caregivers, their families and the wider society as a whole.

The omission of societal costs obscures cost savings and may result in the prioritization of inferior, less expensive or chronic treatments over groundbreaking treatments. For example, in the early years of HIV/AIDS, non-medical costs incurred by society were as much as 6.5 times direct medical costs.²¹ Similarly, 80% of total costs for cirrhosis and chronic liver disease are indirect costs.²² Importantly, the prevention of HIV can reduce lifetime costs an average of \$1.5 million dollars per case averted.²³ In addition, value of hope estimates defined specifically as the current consumption of future survival are a further omitted source of costs. In one study of HIV patients, actual estimates of the value of hope was four times that of standard estimates of this measure.²⁴ Yet ICER's base case, which takes the payer perspective, would not adequately capture these vast costs. These costs must be reflected in value-based pricing to ensure the full worth of new treatments are captured. Another area excluded 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 VF. 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. In addition, the quality adjusted life year (QALY) as a sole determinant of value is insufficient in capturing the various aspects of the value a chronic or curative treatment provides and needs to be supported by other qualifiers, relevant criteria, and evidence such as additional elements of value and other outcomes considerations.

To further incorporate a societal view, ICER should expand the Membership Council to include several stakeholders that are currently left out of the vote on net clinical benefit, contextual considerations and value. The current ICER panel as it stands has an overwhelming majority (>80%) of academics and physicians, with a mere handful of patient advocates. This leads to less representative, disconnected votes on value, from a panel that lacks the membership and much needed diversity from the community that is impacted. ICER states that it *“recognizes how vital the patient and clinical expert perspective is to our review process and public meeting, which is why we seek input from patient and clinical experts throughout the report development process, and by including several such experts as active participants as throughout our public meetings. We believe this approach provides members of ICER voting councils with sufficient insight into the patient experience and clinical practice, and do not propose any changes.”*²⁵ We would argue that this assumption is insufficient for decision-making failing to reach the level of inclusiveness that ICER states in their introduction wherein *“all stakeholders who have an interest in an HTA topic should be included in the review and deliberation process”*.²⁶ ICER has an opportunity to include much needed patient and other relevant perspectives into their assessment process by including more votes on value from those who are affected.

ICER should focus their reports and press releases on cost-effectiveness analyses based on varied thresholds that reflect real world preferences. Moving forward ICER has decided to standardize their cost effectiveness thresholds to range from \$50,000 to \$200,000 with no variation for rare or

ultra-rare diseases due to ICER concerns of equity and what they perceive as mischaracterization of ultra-rare conditions. However, patient approval for variations in thresholds has been well studied in certain situations. One study concerning the value of life in terminal care found that current methodologies for valuing a life either undervalue or omit those end of life costs.²⁷ Other HTA decision makers have responded to such real world considerations by raising the cost-effectiveness thresholds to make provisions for these diseases and patient circumstances. NICE, for example, evaluates drugs for rare diseases on a sliding scale which can be as much as ten times higher than the normal NICE limit. NICE has the discretion to consider whether NHS should accept a higher opportunity cost threshold than normal when a treatment may offer equivalent health gain and displacement but have other value elements that the QALY cannot capture.^{28,29} Therefore, a cost-effectiveness threshold that has the flexibility of varying with context of disease rarity, severity, and impact on particular stage of life would better reflect real-world preferences. Moreover, society may be willing to pay more than what ICER deems cost-effective, and in any case, threshold values should be updated over time to reflect inflation and society's evolving preferences.³⁰ In this regard, it is noteworthy that as cited in our last comments, the current \$50,000 threshold from 1972 if adjusted for inflation would be equivalent to \$307,000 today, more than \$100,000 more than ICER's proposed maximum threshold.³¹

ICER assessments need to reflect the full value to taxpayers if they are to be used by public decision-making bodies. Inaccurate assessments which only focus on direct costs to payers and utilization of the narrow outcome measures (which has its own limitations) can lead to decisions on the wrong treatments, which can have unintended or wider consequences on patients and society. For example, the outcome that ICER uses, QALYs and equal value of life-years gained (evLYG), omit the societal public health benefits in areas such as the potential for disease eradication and reduced infection rates in HIV and Hepatitis C virus (HCV). Janssen recently partnered with Oklahoma Health Care Authority for its schizophrenia medication, Invega Sustenna[®] and Invega Trinza[®], which not only demonstrated superiority in preventing relapse in schizophrenia patients but also lengthened the time to first psychiatric hospitalization or arrest and/or incarceration. Recognizing the distal effects of treatments not only to the health care system but the wider economy as a whole, Oklahoma became the first state to win approval from CMS to enter results-based agreements with manufacturers.³² These reflections of full value on other areas of the US economy are especially important in treatments for rare diseases, such as HIV and oncology as well as more common diseases. It will be important for ICER to consider these wider considerations for their assessments to be both valid and pertinent in the current environment.

ICER's budget impact analyses should be context-specific and reflective of society's preferences. In the 2020 Value Framework ICER has decided to extend the time period of FDA approved drugs for its analyses from two to five years, which is based on an estimate of the total US eligible patient population, with a 20% uptake each year over five years to reach 100% of those eligible.³³ However, ICER's approach of providing a national budget analysis is flawed in a number of ways. For one, it is misleading for decision-makers as no single U.S. payer shoulders the responsibility of coverage for the entire nation. Payers need the autonomy to perform their own budget impact modeling specific to

their particular population epidemiology, age, and socioeconomics: ICER budget impact analysis lacks this contextual relevance. Moreover, ICER's budget impact analysis tends to grossly overestimate the population that will receive the treatment, and therefore exaggerates the likely budget impact. This limitation in patient population estimation was noted in a study examining ICER's budget impact forecasts, finding that ICER's population estimates exceeded RWD by 7.4 to 54 times.³⁴ ICER should consider modifying this methodology to avoid vastly overestimating budget impact; its yearly 20% uptake is not reflective of real-world situations. In addition, ICER's decision to base its budget impact threshold on historical FDA approval and drug share of healthcare spending is arbitrary and not reflective of society's preferences. This approach to judging whether a therapy's budget impact is acceptable is not dependent on its health gains but rather on the number of total therapies approved recently under the assumption that the prior years' approvals are a valid basis for future years. It also capriciously values health gains more acceptable if delivered with one type of intervention versus another, such as surgeries vs drugs and penalizes drugs that would bring large health gains to many people, thereby disincentivizing innovation for cures and other breakthroughs for large populations.

3. ICER needs to demonstrate its relevance by enforcing the grand bargain.

Foremost in ICER's VF 2020 changes is enforcing the grand bargain that will genuinely allow ICER to reach its goal of objectively balancing innovation, fair access and appropriate pricing in its assessments. In keeping with this, as ICER has said regarding PCSK9s, *"When a manufacturer is willing to responsibly price an innovative medicine in line with its clinical benefits, payers should reciprocate by removing the hurdles that can prevent patients from getting the drug."*³⁵ The grand bargain is a commitment from manufacturers that they will price FDA approved drugs according to the value that they bring, and, in return, payers will remove patient barriers to access. A similar bargain is struck in the Medicaid program. There, pursuant to the Medicaid Drug Rebate Program, manufacturers agree to mandatory discounts in exchange for state participation of guaranteed coverage for all drugs approved by the FDA.³⁶ In contrast, the "grand bargain" on value is at most a theoretical, academic exercise at present. ICER could and should serve as a resource to hold payers to account for their role in the grand bargain by rating payer coverage and access policies, tracking progress for meaningful patient access for products with value-based prices, and other objective mechanisms to drive accountability.

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 offer greater relevance through advancing the practice of value assessment that incorporates RWE that matters, sets the societal perspective as the base case and enforces the grand bargain.

Sincerely,

A handwritten signature in black ink, appearing to be 'Bill Guyer', with a stylized, overlapping loop structure.

Bill Guyer
Senior Vice President and Head of Medical Affairs

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October 16, 2019

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Re: ICER 2020 Value Assessment Framework: Proposed Changes

Dear Dr. Pearson,

GlaxoSmithKline (GSK) appreciates the opportunity to provide comments on ICER's proposed changes for its 2020 Value Assessment Framework (VAF). GSK is committed to engaging with US value assessment organizations, such as ICER, 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 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; and
- 5) Support health policy decision-making that fosters innovation.

GSK commends ICER's commitment to improving its VAF and processes. However, we believe that proposed changes for the 2020 VAF update must be broadened further to better reflect the value of innovative health technologies to US patients, caregivers, providers, and payers. For ease of review, we have focused our comments to four core themes including: *(1) Need for Broader Approaches to Capture Patient, Caregiver, and Provider Values Within Other Benefits or Disadvantages and Contextual Considerations; (2) Formal Process and Guidance on Incorporation of Real-World Evidence (RWE) Is Needed; (3) Expansion Beyond Traditional Methods to Holistically Quantify Additional Dimensions of Value Is Essential to US Value Assessment; and (4) Additional Issues for Broad Consideration.*

1. Need for Broader Approaches to Capture Patient, Caregiver, and Provider Values Within Other Benefits or Disadvantages and Contextual Considerations

GSK commends ICER for the proposed use of a Likert-scale voting structure to account for "Other Potential Benefits or Disadvantages and Contextual Considerations" as part of the draft 2020 VAF update (ES4-ES6, p 28-34). This proposed revision is a positive step towards characterizing important elements of healthcare value with increased transparency and methodological rigor. Nevertheless, in recognition of well-documented claims that the patient and provider perspectives are not adequately reflected in ICER VAF evaluations, we urge ICER to more formally incorporate the priorities of patients and caregivers through routine engagement with patient and provider advocacy organizations as part of the appraisal committee

review and voting process (Mendez 2019, PIPC 2018, Kanaskar 2019, PMC 2017). We are also mindful that ICER has proposed to create a new section on Patient Perspectives (p 39, lines 1392-1395). We strongly support this proposal and recommend the formal inclusion and report of evidence from studies of patient preference and disease burden, inclusive of summaries of qualitative information, in all ICER value assessments. In addition, we recommend that ICER further expand the voting questions in this section to explicitly include separate questions for “each value element” prioritized by patients, caregivers, and providers during ICER’s engagements on topics. Broader qualitative characterization of value elements important to patients, caregivers, and providers with specific recommendations from ICER for future evidence generation will reinforce the necessity for research on other benefits or disadvantages and contextual considerations for quantitative incorporation in future value assessments.

GSK does not support ICER’s proposal to formulate one question on “health loss without this treatment,” *in lieu* of separate questions that focus on “severity of illness” and “lifetime burden of illness” as these are important individual value elements within the 2017–2019 VAF (Appendix, Figure 1; ICER VAF 2017–2019). The proposed singular question on relative health loss as reflected by the draft of ICER’s economic analyses of proportional and/or absolute quality-adjusted life-year (QALY) shortfalls (Draft 2020 VAF: p29, line 1121, table row 5)—is akin to an elicitation of the committee members’ preferences for standard of care. It is our belief that clinical unmet need and the lifetime burden of the illness born by patients, caregivers, providers, and society must be evaluated holistically and reflective of the condition and indications being evaluated rather than solely reliant on economic or QALY calculations. GSK urges ICER to reconsider its proposal to remove categories within this section, which qualitatively assesses the clinical unmet need, in terms of disease severity and lifetime burden of illness.

Recommendations:

- *GSK urges ICER to preserve questions and categories that explicitly assess the clinical unmet need, disease severity and lifetime burden of illness within “Other Potential Benefits or Disadvantages and Contextual Considerations” report section and for appraisal committee voting.*
- *GSK urges ICER to formally include for appraisal committee voting the additional value elements and questions from patient, caregiver, and provider perspectives that are identified during ICER engagements with patient and provider groups and review of patient-generated evidence (i.e., patient preference studies, disease burden survey, etc).*
- *GSK urges ICER to consider a standard communication template for public release of draft reports and final reports that equally presents contextual considerations from patients, caregivers, and providers relative to clinical and economic outcomes.*

2. Formal Process and Guidance on Incorporation of RWE Is Needed

GSK acknowledges the importance of incorporating real-world evidence (RWE) in ICER evaluations and recognizes ICER’s reaffirmation of their “ongoing commitment to use existing RWE” (Draft 2020 VAF: ES1-2, p 5, p 24). RWE has an ever-growing importance in the US healthcare system, with applications extending to identification of early treatment milestones, clinical trial design and execution, post-marketing studies, and indication expansion (Ahmend 2018, Reynaldo 2018). The US Food and Drug Administration (FDA) has already implemented policies for the submission and use of RWE by manufacturers thereby recognizing the tremendous value RWE can add (US FDA 2019). It is apparent that RWE will likely play an

expanded key role in drug approval and healthcare decision making as manufacturers continue to advocate for broader inclusion of RWE in the FDA’s regulatory evaluation process (Brennan 2019). More recently, the Bipartisan Policy Center (BPC) Report, *Expanding the Use of Real-World Evidence in Regulatory and Value-Based Payment Decision-Making for Drugs and Biologics*, outlined key policy recommendations for the use of RWE that included “clearing barriers to the access and use of real-world data to provide an evidence base for regulatory evaluation and value-based payment programs, expanding opportunities to use new data sources and approaches, and advancing new models of collaboration among payers, manufacturers, regulators, clinicians, and—most importantly—patients” (Bipartisan Policy Center 2019).

As our healthcare and regulatory systems continue to understand and refine the definitions, implications, and value of RWE, it is vital that ICER’s 2020 VAF methodology embody the broadening evidentiary criteria for regulatory approval. ICER’s methods should reflect and accommodate appropriate inclusion of RWE in its assessments in a rigorous, methodological, and transparent manner. GSK encourages ICER to increase transparency around the methodology utilized when considering the use of RWE for an assessment. Details regarding the methods, determinants, and processes ICER will use to “assess the internal and external validity of RWE” studies are critical for stakeholders and should be defined in a transparent manner. Further details around methodologic protocols ICER will use when evaluating the quality and validity of RWE will assist manufacturers in understanding how RWE submitted for ICER’s consideration are evaluated and inform future evidence generation. ICER may consider adopting a formal guidance on RWE for manufacturers, similar to FDA’s Guidance for Industry when submitting RWE (FDA 2019).

GSK acknowledges the importance of collaborative partnerships in advancing understanding of the effectiveness of therapies beyond the clinical trial setting. However, ICER has proposed to generate real-world data for the sole purpose of complementing published data sources during its value assessments. Given the timing of ICER assessments, it is unlikely that ICER-led real-world studies would be afforded the rigors of scientific peer-review prior to inclusion as inputs in ICER assessments. We urge ICER to thoughtfully consider methodologic and process guidelines for RWE developed by the Joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR)/the International Society for Pharmacoepidemiology (ISPE) Special Task Force on RWE (Berger 2017)—including recommendations for stakeholder (e.g., patient, manufacturer) consultation and public study registration and publication. As peer-review is the current standard of transparency and methodologic rigor, many stakeholders will struggle to reconcile the validity of the value assessments results which incorporate RWE that has not been peer-reviewed.

Recommendations:

- *GSK recommends that ICER develop and implement a transparent, systematic approach to incorporate RWE into its future reviews. This includes clearly defining and delineating criteria for determining the internal and external validity of RWE for consideration in its assessments as well as timing of updates to completed reviews based on new RWE. ISPOR and ISPE have developed methodological and process standards for RWE (e.g., ISPOR’s Good Practices for Outcomes Research reports); ICER could use these standards to assess the quality of individual studies.*
- *GSK recommends that ICER develop a formal guidance on RWE, similar to FDA’s Guidance for Industry when submitting RWE, and actively engage manufacturers and other stakeholders for input (FDA 2019). GSK requests that in instances where RWE data are excluded by ICER, a detailed explanation of the reason for exclusion is provided to the manufacturer and summarized in the evidence report vis-à-vis the chosen validation criteria. GSK recommends that ICER consider including a section describing RWE studies and evidence that are excluded from the evaluation and highlight gaps that may be addressed in future studies. This additional section may be a component of*

an existing section (e.g., a subsection of the Comparative Clinical Effectiveness and Comparative Value sections) or a separate section devoted to the RWE base to allow readers to better understand the full range of potential outcomes observed.

- *GSK recommends for ICER-led initiatives to generate real-world data, ICER provide a detailed processes and opportunities for stakeholder review, such as establishment of an external protocol review committee (external steering committee), dissemination of protocols, analysis plan, data integrity process, final study report, and peer-reviewed publication.*

3. Expansion Beyond Traditional Methods to Holistically Quantify Additional Dimensions of Value Is Essential to US Value Assessment

As noted in previous correspondence with ICER and in section 1 above, GSK recommends that ICER expand the inclusion of both quantitative and qualitative patient and caregiver evidence. ICER noted that similar feedback was also received from other stakeholders but *did not* include any proposed changes in terms of adding quantitative measures of value, citing “strong conceptual and practical reasons not to add quantified additional dimensions of value into our cost-effectiveness analyses at this time” (Draft 2020 VAF: ES3, p 12-14).

The ISPOR Special Taskforce on Value Assessment Frameworks defines additional elements of value such as real-option value, the value of knowing, the value of hope, insurance value, equity, and scientific spillovers (Lakdawalla 2018, Garrison 2016, Garrison 2017). The importance of accounting for these additional dimensions of value have been recognized by numerous other stakeholders (IVI 2019, Lakdawalla 2017). ICER itself has commented on the importance of these additional value dimensions in its “Valuing a Cure” initiative (ICER 2019a, ICER 2019b). International stakeholders who participated in ICER’s recent webinar to discuss its Valuing a Cure Initiative, including representatives from health technology assessment (HTA) organizations, payers, manufacturers, non-profit organizations, patient advocacy groups, and policy focused organizations, unanimously agreed that ICER should incorporate these additional dimensions of value in the methodology for evaluation of *all* therapies (ICER 2019c). We concur with other stakeholders and strongly believe that consideration of these other dimensions of value should not be reserved for SSTs alone, but should also be included in ICER’s 2020 VAF update and applied broadly for all therapies evaluated by ICER.

GSK recognizes the challenge in quantifying these additional dimensions of value, given the highly individualized perspectives of these elements and risks such as “double-counting” the value of a therapy when considering a multitude of elements. However, considering the inherent importance of these value elements, their exclusion would potentially underestimate the true value of an intervention to society and potentially disenfranchise patients and their caregivers. The Innovative and Value Initiative (IVI) noted in its comment letter response to ICER’s Valuing a Cure Initiative that “ICER views new value elements as *additive*, when in fact [research demonstrates that] concepts like ‘insurance value’ and ‘value of hope’ are *corrective*” (IVI 2019, Lakdawalla 2017). It is critical that these additional dimensions of value are formally acknowledged and incorporated by ICER moving forward.

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. As such, GSK re-iterates our recommendation for ICER to empirically pilot new approaches which may more efficiently capture aspects of value relevant to patients and society.

Recommendation:

- *GSK reiterates our call to action for ICER to empirically pilot new approaches, such as the Burden Augmented by Deadliness and Impact (BADI) (Caro 2018) and reevaluate the use of multi-criteria decision-analysis (MCDA) (Phelps 2017, Jit 2018) or extended cost-effectiveness analysis (ACEA/ECEA) (Verguet 2016).*

4. Additional Issues for Broad Consideration***4a) Measures of Health Gain (Draft 2020 VAF Section 3.1)***

GSK appreciates ICER's reaffirmation of its commitment to include a broad perspective on cost-effectiveness in all assessments by measuring both a treatment's QALY gained and complementary Equal Value of Life Years Gained (evLYG) in order to decrease potential risk of discrimination amongst patient groups. However, GSK contends that any quantification of healthcare value in the absence of patient and caregiver perspectives and evidence on the most important benefits, risks, and trade-offs, is fundamentally incomplete. The voices and perspectives of patients and caregivers are truncated in ICER's current proposed methodology. Healthcare value extends beyond effectiveness of therapy and includes financial burden, psycho-social burden, and family spillover benefits, none of which are adequately captured by measurements of QALY or evLYG.

As a company committed to advocating for the meaningful inclusion of patients and caregiver perspectives and evidence in value assessments, GSK reiterates our position and recommendations submitted as part of GSK's comments during the Open Input Period.

Recommendation:

- *GSK recommends ICER re-explore value assessments using alternative approaches as outlined in Section 3.*
- *GSK also recommends that ICER continue to broaden patient engagement and representation in ICER's value assessment process and expand the inclusion of qualitative patient and caregiver evidence, including patient-reported outcomes, psycho-social burden, and preferences data, into its value assessments, as described in Section 1.*

4b) Evidence Rating Matrix (Draft 2020 VAF Section 3.2)

As noted in our previous correspondence, GSK has serious concerns regarding the utility of the ICER Evidence Rating Matrix (ERM) to adequately assess the quality and certainty of clinical evidence for emerging and innovative therapies. Despite ICER's proposed adaptation for expansion of the evidence ratings which fall within the "moderate certainty domain," there is still an underlying fundamental flaw with the use of ICER's ERM. GSK acknowledges that the ERM is designed to provide stakeholders with a concise summary rating of evaluated therapies, and the proposed changes are also intended to provide further transparency and detail around this rating. Nevertheless, the ERM's level of certainty is based on a "conceptual confidence interval" of existing evidence (Ollendorf 2017). The five domains of the ERM that are used to anchor the "conceptual confidence interval" (i.e., Level of Bias, Applicability, Consistency,

Directness, and Precision) disadvantages the evidence ratings for any conditions wherein evidence generation is challenged by the inherent uniqueness of the disease. This may impact at least 25% of ICER's last 21 evaluations conducted since 2018.

In addition, ICER states that revisions will retrospectively be made to previous ratings in ICER reports from 2017–2019 to match new Evidence Rating categories, but will not reflect any new evidence that has become available since the time of the initial report. Failing to incorporate new evidence when updating the evidence ratings to align with the new rating categories will inaccurately represent the current value of products and risks being misinterpreted by readers who may not be aware of new evidence that has become available but not utilized when determining the new evidence ratings. Ultimately, this may undermine public confidence in the validity and quality of ICER generated ratings and be perceived as a disservice to the stakeholders that ICER seeks to serve.

Recommendations:

- *GSK recommends that ICER discontinue the use of its ERM for assessment of orphan diseases and indications with small patient populations (e.g., <200,000 patients), to account for the challenges of evidence generation in these patient groups.*
- *GSK recommends 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.*
- *GSK recommends that any revisions to existing evidence ratings include newly available evidence since the time of the initial evaluation. At minimum, if no new evidence has been reviewed, ICER should clearly and transparently label the revised evidence tables noting when they “do not take into account/reflect any new evidence published after the original release date of the report.”*

4c) Cost-Effectiveness Threshold Ranges (Draft 2020 VAF Section 3.3)

GSK recommends additional clarity around ICER's proposal for cost-effectiveness thresholds in the 2020 VAF Update. ICER has stated it will “continue to use the range of \$100,000–\$150,000 per QALY and per evLYG in presenting value-based price benchmarks” and proposes to “provide a broader range of results [using cost-effectiveness thresholds] symmetrically around this range, from \$50,000–\$200,000 per QALY/evLYG. We believe this is a broad enough range to accommodate the needs of decision-makers in the US to think about their own desired interpretation of cost-effectiveness thresholds.” GSK believes that critical needs of the US healthcare decision-makers—patients and caregivers, providers, payers, and policy-makers—are not adequately served by the cost-effectiveness threshold approach to value-based price benchmarking, as it assumes that key assumptions to estimate incremental cost-effectiveness ratios are robust enough to support such exercises. The limitation of CEA as the sole tool for price-setting is exceptionally acute in rare diseases and cancers, where dimension of values such as unmet need, disease severity/burden, prognosis, value of hope, and small populations drives and redefines willingness to pay by type of decision-maker (Lakdawalla 2012, Aggarwal 2016).

Recommendation:

- *GSK urges ICER to eliminate the proposed range used for the value-based price benchmarks entirely.*
- *GSK recommends that ICER undertake the identification and validation of specific willingness-to-pay thresholds, as part of multi-stakeholder research studies, using approaches such as conjoint analyses and mixed methods to quantitatively and qualitatively assess US societal preferences.*

4d) Alternative Economic Model Assumptions (Draft 2020 VAF Section 3.6)

GSK supports ICER's proposal to create a sub-section, on "Controversies and Uncertainties" to present stakeholder comments on different economic model variations, relative to the base case model assumptions and outcomes. However, GSK re-iterates our call to action for ICER to adopt more processes and policies that improve transparency. Current guidelines for cost-effectiveness models emphasize the importance of transparency in health economic evaluations and state that "trust and confidence are critical to the success of health care models. There are two main methods for achieving this: transparency (people can see how the model is built) and validation (how well it reproduces reality)." (Eddy 2012). ISPOR's Consolidated Health Economic Evaluation Reporting Standards (CHEERS) report also emphasizes the importance of transparency in health economic evaluations (Husereau 2013). Additionally, the Second Panel on cost-effectiveness in Health and Medicine notes model transparency as a key topic for advancing methods and for improving the use of cost-effectiveness analyses (CEAs) in decision-making, noting the need to create CEAs that are accessible, and understandable, to all users (Neumann 2018).

In ICER's proposed changes to its VAF, it was noted that other stakeholders had also urged "greater model transparency" by "public release of fully executable models," however ICER did not propose any changes in the 2020 VAF update, noting that "involved manufacturers may obtain a working copy of the economic model for review prior to providing public comment on each draft report." We urge ICER to redefine its process for when manufacturers request working copies of economic models, as these are often available at a cost to the manufacturer and access is limited to a short period of time. There also appear to be inconsistencies across ICER's academic modeling groups as to what, if any, fees are required to access an ICER model.

Recommendation:

- *GSK recommends that ICER broaden its efforts to capture stakeholder views on alternative economic model assumptions, beyond the sub-section for Controversies and Uncertainties, to an open source modeling platform and establish multiple stakeholder review periods on the draft and final version of the economic model.*
- *GSK recommends in the short term, that ICER develop a transparent and consistent payment policy with ICER's academic modeling groups regarding access to models.*

4e) Long-Term Cost Effectiveness, Payment Models (Draft 2020 VAF Section 3.7)

ICER states that it will "actively seek information from manufacturers and payers about the potential outline of outcomes-based contracts for scenario analyses in our reports." GSK urges ICER to increase transparency around this methodology, as the current lack of an evidence base to support these methods raises many questions and concerns. Of greatest concern is the broad generalization of a single threshold and set of assumptions underpinning explicit recommendations to consider (or not) an outcomes-based contract for a particular drug or drug class. This assumes a "one size fits all" approach which is not representative of the public or commercial payer decision-making in the United States. Moreover, it is unclear how ICER proposes to set policy recommendations for outcomes-based contracts given wide variations among public or commercial payers in plan size, sector, region, characteristics of the covered lives, diagnosis, and interventions of interest, to name a few.

Thus, some areas that require further clarification on the methods and intent include: the use of scenario analyses to identify varying circumstances in which an outcomes-based contract may be recommended; how ICER will account for the plan to plan variation noted above; and what information ICER will seek from manufacturers and payers to inform these analyses.

Further clarity and detail should also be provided around whether ICER's proposed payment model adaptation for SSTs (Section 2.4) will also apply to all products evaluated utilizing ICER's 2020 VAF. The proposed adaptation for SSTs notes that "at a price at which is greater than 25% of PSA simulations of the base case produce incremental cost-effectiveness ratios above \$200,000 per QALY, we propose to include a policy recommendation that payers and manufacturers view outcomes-based contracting as the preferred method of payment."

Recommendation:

- *GSK recommends that ICER reconsider its proposal to provide contracting recommendations in the context of its evidence reports. Rather, that ICER's analyses and evidence be presented in an unbiased manner which may be used as a component of the evidence compendium considered by decision-makers when making coverage decisions. Further, GSK requests clarification on how ICER intends to consider the range of potential variation across payers, differences in public and private payer dynamics, as well as variations in how contracts are constructed (e.g., outcomes-based).*

4f) Report Development and Public Meetings (Draft 2020 VAF Section 6)

GSK believes that on-going transparency and engagement challenges within the ICER value assessment process may be ameliorated by increased standardization and broader disclosure, as exemplified by the Advisory Committee on Immunization Practices (ACIP) processes and policies previously highlighted in our prior correspondence (ACIP 2019). We believe that the processes of ACIP, may serve as an example for robust stakeholder engagement and transparency. ACIP, the gold-standard by which US vaccine policy recommendations are developed and updated in alignment with innovation and public health priorities, employs external clinical and economic experts to externally validate all draft and final reports as well as make public executable economic model files for review (ACIP 2019). GSK believe that the composition of ICER appraisal committees should include broader representation by members with disease-area expertise, patients and caregivers directly impacted by the indication under review, community providers, and disability advocates. GSK urges ICER to reconsider its position to maintain the status quo on appraisal committee membership.

GSK acknowledges and appreciates the importance of ICER's proposed process to formally re-assess whether new evidence has emerged with an update to its Final Evidence Report one-year after publication. This proposed update aligns with a key domain of "timeliness of updates" outlined by ACIP and will allow ICER to better capture new evidence and support policy decision-making. We urge ICER to prioritize its efforts to improve patient, caregiver, and stakeholder engagement into its VA process per the recommendations below.

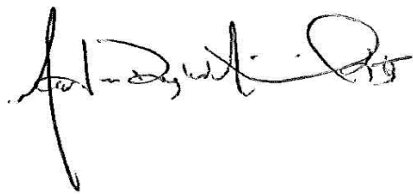
Recommendation:

- *GSK recommends that ICER provide further clarification on how new evidence will be reflected in updated Final Evaluations. GSK recommends that ICER provide transparent methodology for incorporation of long-term, or new data, which may not be consistent with data previously utilized in ICER's methodology (i.e., methodology for structural updates to cost-effectiveness models).*

- *GSK recommends that ICER reconsider the current appraisal committees' membership composition. Expanded inclusion of disease-specific patient groups, disability advocates, clinical and economic academic experts is recommended to complement payer perspectives.*
- *GSK recommends that ICER establish permanent research workgroups for topic/therapeutic areas and expand workgroup memberships to patient representatives as well as other lay and academic stakeholders.*
- *GSK recommends that ICER foster expertise and consistency by assigning permanent topic/therapeutic areas to its US academic collaborators.*
- *GSK recommends that ICER adopt ACIP multi-public meeting approach, providing 2 to 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.*

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

Sincerely,



Martin D. Marciniak, PhD
Vice President
US Medical Affairs, Customer Engagement,
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Appendix:

Figure 1. Contextual Considerations, ICER 2017-2019 Value Assessment Framework (ICER 2017)

Contextual Considerations:

Are any of the following contextual considerations <u>important</u> in assessing this intervention's long-term value for money?			Contextual Considerations
Yes	No	Uncertain	This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
Yes	No	Uncertain	This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
Yes	No	Uncertain	This intervention is the first to offer any improvement for patients with this condition.
Yes	No	Uncertain	Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Yes	No	Uncertain	Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
Yes	No	Uncertain	There are additional contextual considerations that should have an important role in judgments of the value of this intervention: _____ _____

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October 2, 2019

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Submitted Electronically: publiccomments@icer-review.org

RE: 2020 Update to ICER Value Framework

Dear Dr. Pearson:

Haystack Project is pleased to submit its comments to the Institute for Clinical and Economic Review's (ICER's) proposed changes to the ICER Value Framework for 2020.

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. Throughout our comment submission, we refer to RCPC and the Haystack Project collectively as "Haystack."

We recently submitted feedback to ICER during its open input period for the 2020 Value Framework, as well as in connection with proposed framework adaptations for potentially curative therapies. Haystack appreciates ICER's efforts to incorporate our recommendations and concerns into its processes for developing cost-effectiveness reports. We note, for example, that ICER proposes to:

- Seek opportunities to generate new real world evidence (RWE) for incorporation in reviews;

- Add a “Controversies and Uncertainties” section to the cost-effectiveness portion of its reports in order to broaden discussion of alternative model structures and assumptions suggested by manufacturers or other stakeholders;
- Extend the draft report public comment period for class reviews by one week; and
- Create a new “Patient Perspectives” chapter for its reports that will describe the input received from patients, families, and patient organizations, as well as relevant sources of patient-generated evidence.

We remain concerned, however, that patients with rare and ultra-rare conditions or rare cancers will continue to fear ICER reviews as inevitably concluding that the new, life-saving treatment they had hoped for offers inadequate “long-term value for the money.” The proposed framework updates fall short of addressing the challenges patients with rare and ultra-rare diseases and rare cancers face within the context of value frameworks that rely on population-level indices of quality and value. Moreover, ICER’s decision to eliminate the primary “benefit” of previously-implemented framework adaptations for ultra-rare disorder treatments in favor of standardized cost-effectiveness thresholds from \$50,000-\$200,000 per QALY and per evLYG for all reviews could function as a “red flag” for potential investors in the rare disease space. We understand that ICER’s processes and policies will continue to evolve, and urge it to remain mindful of the fact that real lives hang in the balance when “value” reports prescribe or proscribe access to new treatments for serious rare diseases.

Emerging Treatments for Rare and Ultra-Rare Conditions, Including Rare Cancers are Ill-Suited to Early ICER Reviews.

As ICER noted in its proposed changes to the Value Framework for 2020, “there are broad requirements across the US health care system to fund all ‘medically necessary’ care.” Haystack has significant concerns that ICER reviews, particularly those that are completed in advance of FDA approval, will inject an implied exception to the access mandate ICER acknowledges.

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.” Haystack remains 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. 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.

It is now well-recognized that health economic frameworks utilized to assess cost-effectiveness of treatment options for common conditions will, if applied to higher-cost orphan drugs, fairly

uniformly lead to conclusions that an emerging treatment fails to demonstrate cost-effectiveness. 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. 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.” Rushing to review new treatments with methodologies that inherently fail to capture the indicia of “value” for rare disease states hampers ICER’s ability to fulfill its goal.

ICER continues to rely on the 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. 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. 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.

Haystack appreciates ICER’s recognition that individuals with serious conditions could present a situation where it would be impossible for a treatment to reach cost-effectiveness thresholds even if it were offered at a zero price. This could occur if a new treatment results in more time spent in health states that have very high costs and/or a low utility value. We also appreciate that ICER seeks to address shortcomings in QALY associated with rare disease states by cross-

walking quality of life data captured in clinical trials to model inputs and augmenting clinical trial data with real world evidence. We are optimistic that this would permit a more disease-specific analysis and lead to greater validity in and public acceptance of ICER's reports. Unfortunately, disease rarity can make it particularly difficult to accumulate a sufficient body of this additional data to facilitate its incorporation into an ICER review performed in advance of FDA approval.

Novel approaches to ultra-rare conditions and many rare cancers may be less likely to fail ICER's valuations if given time to be used in clinical practice for a sufficient number of years to establish the value demonstrated in FDA pivotal trials translates to real world use and is durable. We expect that the true value of these treatments will not be captured without sufficient time to learn more about how that treatment works in the real world and across different subsets of patients. We remain convinced that the potential harms to patients outweighs any societal benefits from early reviews of rare and ultra-rare disease treatments.

ICER should ensure adequate opportunities to bolster available clinical trial data with real world evidence.

Haystack strongly encourages ICER to ensure that its reviews incorporate all available information on the specific disease state and treatment options for each reviewed therapy. In particular, we urge ICER to gather, give weight to, and incorporate all relevant data, including RWE. The patient community can play a pivotal role in assessing disease burden, and ensuring that all direct and indirect care costs are incorporated into reviews. Patient-reported outcome studies and studies that capture broader patient and family effects of treatment enable insights that are often not included in clinical trials. Similarly, health care claims databases can provide useful information on historic costs of treating a particular disease, including interventions potentially avoided as each new treatment is introduced.

We appreciate that ICER has expressed an interest in collaborating with organizations to generate RWE as it reviews new treatments and urge it to extend its collaborative partnerships beyond payers to include the patient community and provider specialists with expertise in the specific condition.

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

Haystack continues to 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." We strongly believe that the resulting analyses would fulfill ICER's goal of supporting informed decisions between patients and their providers, as well as with their payers.

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 in rare disorders. Haystack believes that strong collaborative partnerships between ICER and the patient community would enable a thoughtful evolution of methodologies that would enhance validity of rare disease value assessments.

Haystack opposes 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 urges ICER to place 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’s addition of the evLYG as an alternative appears to have chosen to eliminate “quality” from “value” altogether. ICER’s own discussion of evLYG, and its example of two cancer treatment options when introducing its use – one with incremental increase in life expectancy accompanied by extreme decreases in quality of life and function – drive home the fact that ICER finds the evLYG to be clearly inappropriate in the context of cancer treatments. The deficiencies inherent to QALY use in assessing treatments for rare and ultra-rare conditions and rare cancers is not counterbalanced with an alternative approach that, like evLYG, removes the patient voice altogether.

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

Haystack appreciates ICER’s willingness to expand its opportunities for patient engagement. We urge ICER to build upon its proposed stakeholder engagement improvements by:

- Including patient and caregiver stakeholders in the process to inform the scoping document and identify outcomes that are of substantial importance;
- Further expanding the comment periods, including the initial open input period, scoping phase, and draft report comment opportunity;
- Partnering with patient advocacy organizations in a proactive manner to encourage generation of RWE and identification of patient reported outcomes;
- Giving greater weight to patient preferences and priorities within its value assessment; and
- Including patients, caregivers, and relevant specialties on review panels.

Haystack appreciates that ICER plans to incorporate a section on patient feedback within each of its reports. While this may be an improvement from previous stakeholder feedback mechanisms, we believe that ICER could more fully integrate the patient perspective into its reports. For example, ICER should also be better able to identify salient factors gathered from patient engagement activities that align with or cut against model inputs or impact report validity. Over time, ICER's methodologies could evolve to enable quantifiable values for disease-specific priorities, rather than relegating patient preferences to a "side bar" discussion

Conclusion

Once again, we appreciate the opportunity to comment on the proposed framework adaptation. 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.

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.

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October 18, 2019

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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 revised value assessment framework for 2020.

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 and caregivers 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 revised value assessment framework regarding methodology, deliberation, and process:

METHODOLOGY / MODEL

The Use of the QALY in Value Assessments Impacting Chronic Diseases Like Migraine is Discriminatory and Should be Replaced by a Patient-Centered Methodology.

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. For the migraine community, 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.

Future ICER Value Assessments Should Consider the Beneficial Cost Impact of Reducing Co-Morbid Conditions and Use Real World Evidence in Such Considerations.

HMPF supports ICER's recent recognition of the importance of real-world evidence (RWE) and looks forward to its use in future reports in order to more accurately represent value to the patient. We agree that RWE is a better source in actual model input data rather than randomized clinical trials that include a largely unrepresentative subtype of younger patients without a diversity of backgrounds and ethnicities or comorbidities.

With that in mind, ICER's cost assessment must also 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

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

estimated at \$5.4 billion in the United States in 2015, total costs associated with migraine and co-morbid conditions *exceeded \$40 billion*.³ 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.⁴ 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 – using real world evidence - must be factored into the value assessment.

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

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 to episodic headache where patients are not symptom free in-between attacks.⁵ This is currently not reflected accurately in ICER reviews.

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.

The Revised Framework Continues to Inadequately Address Vulnerable Patient Populations Like Persons Living with Cluster Headache.

HMPF was greatly disappointed by ICER’s seemingly arbitrary limitation of the proposed framework to assess the value of rare disease therapies to include those diseases with 10,000 patients or less. This patient population cohort size corresponds to no accepted definitions of rare or ultra-rare diseases but was justified by ICER stating that it was “modestly higher than the threshold used in the EU.”⁶

³ Id.

⁴ 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/>

⁵ Lampl et al, “Interictal Burden Attributable to Episodic Headache: Findings from the Eurolight Project,” Journal of Headache and Pain, Feb. 2016.

⁶ ICER Revised Framework.

Of particular interest to the migraine community is the impact this might have on therapeutic options available to cluster headache (CH) patients. Cluster headache is a primary headache syndrome that is under-diagnosed and in many instances under-treated. The pain produced during a cluster headache is more severe than that generated by any other primary headache. Cluster headache is very stereotyped in its presentation and is fairly easy to diagnose with an in-depth headache history.

Cluster headache is also recognized by the National Organization of Rare Diseases (NORD) as an uncommon form of primary neurovascular headaches. CH are the most painful form of headaches, described as searing, burning, and stabbing. CH is divided into both episodic and chronic, where episodic cluster headache patients experience 1 to 4 short headaches per day that can individually last between 15 and 120 minutes per attack. These attacks (cluster periods) last for weeks or months and are separated by months or years of remission periods where the patients are pain-free. Chronic cluster headache patients suffer without remissions for 1 year or more or with remissions so brief they do not even span a month. Less than 20% of cluster headache patients have the chronic form. There is no cure, and treatment is determined on an individual basis – making access to a wide variety of treatment options critically important to this population.

PANEL COMPOSITION / DELIBERATION / INPUT

ICER Should Allow for Both an Appropriate Disease Specialist and Disease-Impacted Patient or Caregiver to Serve as Voting Members.

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 or caregiver 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 or caregiver 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 or caregiver that broadly and faithfully reflects the patient perspective in the assessed disease state.

Finally, with regard to process we do not agree that voting should occur prior to the roundtable discussion portion of the public meeting. The discussions in the afternoon, after the voting took place, informed several voting members who indicated during last year's migraine review that they would have reassessed their vote had they had the additional information gleaned in the afternoon session. To vote prior to that testimony makes such testimony moot and inconsequential to the outcome. We encourage ICER to allow voting members to vote only after all information is provided at the conclusion of the public meeting.

ICER Should Provide Greater 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.

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.

Alliance for Balanced Pain Management
Alliance for Patient Access
Association of Migraine Disorders
Clusterbusters
Coalition For Headache And Migraine Patients (CHAMP)
Danielle Byron Henry Foundation
Global Healthy Living Foundation
GoldenGraine
Hope for Migraine Community
The Migraine Diva
Migraine Meanderings
Miles for Migraine
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JANSSEN SCIENTIFIC AFFAIRS, LLC

Response to Public Comments on: ICER's 2020 Value Assessment Framework: Proposed Changes

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COMMENTS

At Janssen, we are dedicated to delivering transformational medical innovation that can change the trajectory of health for humanity. We are committed to developing a more results-based healthcare system that delivers greater access to care at more manageable cost and, most importantly, better health for all.

That is why it is important to voice our concerns about ICER's proposed changes to the methods it uses for determining the value of a medicine, as presented in its 2020 Value Assessment Framework.¹

Here are our most important concerns:

- 1. ICER misrepresents evidence, causing the value of medicines to appear diminished. This undermines its aspiration to be an impartial judge of value.**
- 2. ICER continues to use measures of patient outcomes that discriminate against the most vulnerable of populations: the elderly, disabled, and seriously ill.**
- 3. ICER's focus on cost-effectiveness analyses devalues patient and physician viewpoints in determining the value of a new medicine.**

We are joined by a growing group of patients, advocates, and other stakeholders who have expressed their apprehension about the effects of ICER's methodologies and ICER's lack of accountability and oversight, calling into question its aspiration for a "fairer" healthcare system.

We explain our concerns below.

ICER misrepresents evidence, causing the value of medicines to appear diminished. This undermines its aspiration to be an impartial judge of value.

The safety and efficacy of a new medicine are anchored in evidence, most notably the clinical data collected from human volunteers by independent investigators during carefully run trials. Janssen, as a research-based biopharmaceutical company, provides data, designed in conjunction with the U.S. Food and Drug Administration (FDA) and other global health authorities, about a new medicine or a new use for an existing medicine that serve as the foundation for decisions on approval and labeling during a diligent review by regulatory experts.

In the spirit of cooperation and scientific exchange, Janssen has provided relevant data to ICER to assist with its public commentary and product reviews. However, we are concerned that ICER's interpretation of clinical data is at odds with the scientific conclusions issued by the FDA.

For example, ICER's views and subsequent ratings of the clinical assessment of rivaroxaban (Xarelto®) are divergent from the conclusions of the FDA. This misrepresentation by ICER raises red flags about its comparative effectiveness methods and motives. Our concern is further compounded by the fact that ICER does not have accountability or oversight for the consequences of its recommendations.

Here are the facts:

In October 2018, rivaroxaban, when used in combination with aspirin, received FDA approval to reduce the risk of major adverse cardiac events (MACE), including cardiovascular death, myocardial infarction, and stroke, in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).² The FDA's approval was based, in large part, on results from the pivotal COMPASS trial, where treatment with rivaroxaban plus aspirin reduced the risk of MACE by 24%, compared with aspirin alone.³

The COMPASS trial met its prespecified criteria for superiority for the primary endpoint: reduction of MACE in the trial population. As COMPASS continued, the evidence for the combination's beneficial effects was observed to be sufficiently compelling to the point where the study's Independent Data Monitoring Committee recommended that the trial be halted about 1 year earlier than planned based on the prespecified interim analysis plan.⁴ In that recommendation, the Committee cited both the overwhelming efficacy of rivaroxaban plus aspirin for prevention of MACE, including myocardial infarction, stroke, and cardiovascular death, in patients with CAD or PAD, and the large body of safety evidence gathered during COMPASS and earlier clinical trials. This decision was also based on ethical grounds, as withholding potentially life-saving medicine from patients could have detrimental effects. Patients were subsequently offered rivaroxaban in an open-label extension study.

Contrast this with ICER's evaluation of the same data on rivaroxaban. ICER criticized evidence from the COMPASS trial as "inadequate" and mischaracterized the early ending of the study as contributing to "residual uncertainties regarding the true clinical benefit" of treatment with rivaroxaban plus aspirin.⁵ ICER's criticism of the shortened COMPASS study was noted in its downgrade of the overall evidence rating for rivaroxaban.⁵ This downgrade took place despite the positive body of evidence that led the FDA to decide that the benefits of the combination far outweighed the risks.

The ICER Integrated Evidence Rating™ itself is concerning and is emblematic of deeper issues about its commitment to transparency and clarity. In communicating a judgment about the value of a medicine, ICER uses its own idiosyncratic rating matrix that summarizes results through an overlapping array of letters and symbols: A, B, C, D, B+, C+, C-, C++ (new rating), and P/I. This system is confusing, as some of its ratings span a range of levels of incremental benefit. For example, a B+ rating implies anywhere from a small to a substantial net health benefit for a given treatment, which makes interpretation difficult. ICER's approach to representing and rating evidence is neither clear nor transparent, and this has potentially high stakes for patients.

Moving on to our next concern:

ICER continues to use measures of patient outcomes that discriminate against the most vulnerable of populations: the elderly, disabled, and seriously ill.

We at Janssen believe that each patient's life is equally valuable. Therefore, we fundamentally disagree with ICER's continued reliance on quality-adjusted life-years (QALYs) for analyses in the United States.

Among many documented shortcomings,^{6,7} QALY analyses underestimate the value of treatment for elderly, disabled, and most seriously sick patients, in other words, those with the greatest unmet medical needs. For example, the QALY by definition assigns a lower value of a year of life for people with disabilities or serious diseases since they will never reach "perfect" health. In addition, older people are disadvantaged because they have fewer years to accumulate a treatment benefit compared with younger people.

We are not alone in sharing these concerns. In June 2019, the Partnership to Improve Patient Care, representing more than 50 organizations of physicians, nurses, advocates, and patient and caregiver groups, posted similar concerns, asking ICER "not to rely on the use of QALYs and other discriminatory metrics that treat patients as averages."

Further, we at Janssen do not support the use of ICER's "new," unvalidated measure, the "equal value of Life Years Gained (evLYG)," which quantifies only the benefits from reduced mortality. The underlying concept around the evLYG is more commonly known as "life-years gained," a measure found to be deficient nearly 50 years ago and which the QALY was developed to improve.⁸ ICER's choice to revert back to the evLYG contradicts its stated objective to include the patient perspective in all steps of the valuation process.

We are further concerned that ICER references the World Health Organization (WHO) when setting its cost-effectiveness thresholds, which reflect the cutoff of the maximum value of 1 year of human life (eg, \$150,000). ICER is being selective here by ignoring the WHO recommendation that "cost-effectiveness thresholds *never* be used as a stand-alone criterion for decision-making. Above all, the indiscriminate sole use of the most common threshold – of three times the per-capita GDP [gross domestic product] per DALY [disability-adjusted life-year] averted – in national funding decisions or for setting the price or reimbursement value of a new drug or other intervention must be avoided. WHO-CHOICE has never recommended this practice."⁹

ICER's recommended approach to determine a "value-based price" will ultimately have serious effects on patients, whose access may be limited to situations where the value of a new drug meets ICER's predetermined thresholds. Not only do patients with rare diseases fear that thresholds will work to their detriment, but patients with common chronic conditions are likely to suffer as well. Case in point: a 2019 study determined that, if policies based on the ICER budget threshold approach had been applied to atorvastatin, the widely used lipid regulator, there would have been 72,195 more major vascular events and 18,771 additional deaths in the period from 1997 to 2012.¹⁰

ICER's continued use of flawed approaches to determine a value-based price will, in our view, result in worse outcomes for patients, especially for those who are older, disabled, or seriously sick.

The third concern:

ICER's focus on cost-effectiveness analyses devalues patient and physician viewpoints in determining the value of a new medicine.

Janssen believes that medical decisions belong in the hands of patients and their physicians. We also believe that while the safety and efficacy of a medical intervention are paramount, all of those affected by a medical decision should have objective, evidence-based, and well-understood data on the value of that intervention, be it a medicine, device, surgery, or hospital stay.

Cost-effectiveness analysis (CEA) is only one tool that can help inform the value of a healthcare intervention, as it has serious limitations as described above. We believe value should be based on a broader view of the effects that the intervention will have on patients and their families.

Currently, ICER uses the results of its CEA to directly recommend the price of a new medicine. This stands in contrast to the 2016 findings of the Second Panel on Cost-Effectiveness, which states that using CEA in value-based pricing is an area for future research¹¹ and thus is inappropriate to use *now* to calculate prices. Many complex factors affect value-based pricing decisions, such as the long-term impact of treatment on patient health and caregiver burdens, the societal benefits of a healthier population, and the high costs of research efforts to develop next-generation therapies. These factors are important considerations in determining the overall value of all interventions—including vaccines, medicines, diagnostics, devices, surgeries, and hospital stays—to improve patient outcomes.

CEA alone should thus *never* be considered a substitute for thorough and personalized medical decision-making. We firmly believe that ICER's current proposed approach systematically underestimates the full value of therapies to patients, both as individuals and as members of a larger, interconnected society. We also believe that ICER's reliance on CEA encourages access restrictions that could have potentially serious effects on the quality and length of patients' lives. In addition, ICER's framework does not consider a critical driver of patients' out-of-pocket costs and overall spending in the United States, namely health insurance design.

Patients first: the dialogue on access to transformational medicines must keep the patient at the center.

Given both the concerns raised about ICER's misrepresentation of evidence and the other issues related to ICER's methodologies as detailed in this response, Janssen urges those who reference ICER analyses to keep in mind that, in our view and in the views of others:

- ICER's Integrated Evidence Rating™ has misrepresented meaningful advances provided by new medications versus the standard of care, and the proposed changes will add further confusion.
- ICER's use of QALYs places a numerical value on a human life and discriminates against the elderly, disabled, and most seriously sick patients.
- ICER takes a very narrow perspective when considering value that does not appropriately consider patient, caregiver, and physician viewpoints, thereby systematically underestimating the value of medicines to individuals and society.

At Janssen, we are concerned about ICER's narrow approach, lack of accountability or oversight for their recommendations, confusing standards, and bias against patients in favor of short-term budget concerns. The proposed changes in the ICER 2020 Value Assessment Framework are not a roadmap to better healthcare. Quite the opposite: these proposals open the door to diminished care for patients today and fewer breakthroughs for patients tomorrow.

In closing, patients are at the heart of everything we do at Janssen. We take seriously the hope our medicines give patients for a brighter, healthier future. We believe that we must move to a healthcare system that puts patients first and genuinely values the individual decisions they make with their physicians. That's why when it comes to determining a medicine's value, we strongly believe that what matters most is its impact on patients. We encourage all stakeholders to put patients' viewpoints first.

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October 18, 2019

Steven, D. Pearson, MD MSc, FRCP
President
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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 540,000 Americans living with the disease,¹ we appreciate the opportunity to provide comments on ICER's proposed changes for its 2020 Value Assessment Framework. The following comments align very closely with the comments submitted by LUNGevity Foundation in June 2019, and while they are specific to lung cancer, we believe that the same concerns and principles should apply to other disease areas as well.

LUNGevity's mission is to improve outcomes for people diagnosed with lung cancer. Our goals are threefold: (1) to accelerate research to patients that is meaningful to them; (2) to empower patients to be active participants in their own 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.

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, as well as the utmost importance of including robust data that represent how the therapies are used in practice.

As we have touched on in previous comments, lung cancer, like many other diseases, is a heterogeneous set of diseases, both in terms of the biology of the diseases and in the experiences of patients living with lung cancer, and as such, any model or framework attempting to make assessments about the disease or treatments for the disease must be flexible enough to accommodate this heterogeneity. We do not believe that the proposed Value Assessment Framework adequately addresses the heterogeneity of lung cancer or the personalized nature of the treatments that are often driven by the presence or lack of biomarkers. Additionally, as stated in earlier comment letters, models based on population-level data or assessments will fall short of accurately reflecting the value of drugs in the lung cancer space. Given these shortcomings, we offer suggestions in our comments as to how ICER can make its model more flexible, comprehensive, and patient-centric to better assess the value of treatments for heterogeneous diseases that impact diverse patient populations.

In summary, we recommend the following to make the ICER model more rigorous and patient-centric:

- A. Provide transparency to model development and a clear pathway for incorporating methodological input and key stakeholder feedback
- B. Include the patient experience in determining the value of a treatment approach.
- C. Incorporate patient-reported outcome/Quality-of-Life metrics along with aggregate metrics, such as QALYs and evLYGs, to quantify the economic impact of precision therapeutics
- D. Incorporate real-world data and real-world evidence about clinical practice
- E. Expand the framework to include the role of precision diagnostics
- F. Allow flexibility in the calculation of budget impact in the Value Assessment Framework

These are discussed in greater detail below.

A. Provide transparency to model development and a clear pathway for incorporating methodological input and key stakeholder feedback

Transparency is an important component of making a value framework model robust and reproducible.

Methodological input: Oncology value frameworks such as the ASCO Value Framework² and Memorial Sloan Kettering Drug Abacus³ have made their methodology transparent. 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. While ICER has already made strides in making their models transparent to manufacturers, we recommend that ICER make its models publicly available to all users. This will ensure that ICER models are accessible to methodological experts in the field who can use and attest to the credibility of the ICER models, thereby increasing acceptability. Furthermore, models should be customizable by stakeholders for use outside of review purposes.

Key stakeholder feedback: Key stakeholders of value frameworks are patients and clinicians.⁴ We commend ICER for providing an opportunity to gather feedback from patients and patient advocacy groups. However, it is unclear how these comments are incorporated into the final model. In addition to the three areas of feedback described in the guidelines document from ICER,⁵ we recommend that ICER provide a mechanism of feedback at the inception of and during the development of a framework. Having patient feedback throughout the development process rather than after the creation of a framework will ensure that both the process and the product are patient-centric.

Clinician input during the model development is also essential to ensuring that predictions of treatment choice made by a value framework are clinically meaningful and take into account the choice of drugs available. Given the rapid evolution of lung cancer therapies (there have been more than 15 new FDA approvals for lung cancer since 2015),⁶ we encourage ICER to include expert clinicians who are advising on the real-world use of the therapies as part of both model development and feedback on the final model. To this end, ICER should be open to revising models based on clinician input.

Recommendation: We suggest that ICER incorporate key stakeholder feedback throughout the model development process and make models publicly available for methodological review and validation.

B. Include the patient experience in determining the value of a treatment approach

With progress in lung cancer treatment, survivors are living longer. It is imperative to incorporate the survivor perspective directly 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 also becoming a disease of the young and the non-smoker.⁷ 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 can 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 The 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. Currently in its third year, 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.^{8,9} 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.¹⁰ Age is an additional determinant of patient preference. Younger (less than 60 years of age) and older (≥ 60 years of age) patients value different aspects of their cancer treatment: younger patients are willing to undergo more aggressive treatments with a higher incidence of side effects as long as those treatments provide a longer PFS.¹¹ Taken together, these results demonstrate that patient experience is very heterogeneous and should be taken into account in value assessment frameworks.

Recommendation: We recommend that ICER incorporate patient experience data (for example, patient preference research) that provides contextual information of the value of the quality and quantity of life a specific treatment provides. Particularly, patient experience data will be of paramount importance in determining the true value of care for a patient, where standard of care may evolve or multiple treatment options exist (such as multiple tyrosine kinase inhibitors for a specific targetable mutation).

C. Incorporate patient-reported outcome/Quality-of-Life metrics into aggregate metrics, such as QALYs and evLYGs, to quantify the economic impact of precision therapeutics

The lung cancer treatment landscape has rapidly evolved over the past five years, with the US Food and Drug Administration 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.^{12,13} The complex nature of this disease requires personalized management plans for patients.¹³ 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.¹⁴⁻¹⁶ Now, more than 20 driver mutations in adenocarcinoma have been identified, among them EGFR, ALK, ROS1, RET, ERB2/HER2 mutations, ERB2/HER2 amplifications, MET amplifications, MET mutations, TRK, BRAF, and KRAS.^{17,18} 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 have 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.^{19,20} This rapid evolution of care has increased the need to rethink the thoracic oncology treatment paradigm, including how to combine or sequence drugs. 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, Neumann and colleagues, in their *New England Journal of Medicine* article, point out that the QALY value typically used by healthcare economists in fact underestimates the impact of a drug.²¹ 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.²² Also, QALY is an aggregate metric and 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. In her *New York Times* blog, ovarian cancer survivor Susan Gubar poignantly captures the inadequacies of QALYs in treatment decisions.²³ 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?” 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.²⁴ In summary, QALYs neither capture the heterogeneity of lung cancer biology nor the breadth of patient experience along the lung cancer continuum.

In the current model, ICER attempts to address these shortcomings by developing and utilizing a new metric, Equal Value of Life Years Gained (evLYG), to complement QALYs. While the addition of evLYGs is a step in the right direction and adds another dimension of measurement to QALYs, it continues to be an aggregate metric and completely misses the mark on capturing patient heterogeneity both from a precision medicine and a patient experience perspective. A life extension-based metric such as evLYG is based on a short-sighted assumption that quantity of life is the main determinant of treatment choice. As discussed in Section B, cost-effectiveness analysis should take into consideration values patients place on the balance between the quality and quantity of life a drug provides. Also, other data sources such as patient-reported outcomes (PROs) can provide highly rich contextual information on how a patient feels and functions on different treatments.²⁵ Following the guidance issued by the FDA on both the collection and the use of PRO data, there has been a steady increase in PRO data collection in clinical trials confirming both the importance and the availability of such data.²⁵

Recommendation: To increase the sensitivity of QALYs and evLYGs, we strongly recommend that ICER incorporate patient-reported outcomes (PROs) and quality-of-life metrics into their framework.

Doing so will help accurately capture the differences in patient perspective along the lung cancer continuum. PROs and QoL measure are quantitative metrics that are captured using validated instruments and in a scientifically rigorous manner. Including these metrics will help make the ICER framework more patient-centric²⁶ and compatible with the tenets of precision medicine. ASCO in their value framework discussion—“[p]atient self-reporting affords the opportunity to understand better the impact of care processes on how patients feel (and can optimize) good clinical practice”—points out the value and role of PRO data in increasing both the patient-centricity and robustness of their value framework model.²

D. Incorporate real-world data and real-world evidence about clinical practice

LUNGevity Foundation supports the use of real-world data in value frameworks. Despite an expansion of clinical trials in global sites, an overwhelming proportion of trial participants are Caucasian (86% in 2014 vs. 92% in 1997).²⁷ While beneficial for registrational purposes, the disproportionate number of Caucasians in clinical trials makes clinical trials 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.²⁸ Furthermore, lung cancer clinical trials often exclude patients with brain metastases and low performance status.²⁹ 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, a pristine clinical trial cohort does not capture the lived experience of a lung cancer patient outside of a trial setting. A recent study demonstrates that real-world evidence can replicate only about 15% of interventional clinical trials, reiterating that clinical trial data and real-world data should be viewed as complementary rather than interchangeable.³⁰

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), it is important to develop strict evidentiary standards for the use of such data. Given the FDA’s recent commitment to develop guidelines for the use of real-world evidence for post-marketing surveillance,³¹ we see ICER’s efforts to incorporate real-world data in value frameworks as timely and complementary.

Recommendation: We encourage ICER to reassess evidence once a drug has been used in clinical practice for a sufficient amount of time to accurately capture the impact a drug has made on the survivor community. At a minimum, we recommend that ICER revisit the assumptions of their model when adequate post-marketing surveillance information is available through real-world data.

E. Expand the framework to include the role of precision diagnostics

Drugs are one component of the larger healthcare system; therefore, focusing value frameworks solely on the cost of medications will likely underestimate the true value of a personalized therapeutic that is effected in a selected patient population. The use of high-quality diagnostic tests with well-established clinical and analytical validity to identify appropriate therapies is tied to better outcomes for patients and prevents harm by avoiding therapies that will not provide benefit to patients.

In this era of unprecedented scientific advancements for the treatment of lung cancer, particularly as we identify new biomarkers and biomarker-driven therapies, the value of a personalized therapeutic is highly contingent on the following assumptions:

1. Availability of a high-quality diagnostic test
2. Use of the test in the selection of the right biomarker-segmented patient population
3. Matching the patient to the right biomarker-driven treatment and, conversely, ensuring that the wrong patient doesn't get treated with the incorrect treatment

The importance of assumptions 2 and 3 can be demonstrated through recent research published in the field of targeted therapeutics. There is a clear survival benefit from access to a companion diagnostic for advanced-stage NSCLC patients before commencing first-line treatment, ensuring that patients get matched to the right therapy.³² In addition, diagnostic biomarker testing may not only impact the right treatment selection, but in fact may also prevent a patient from getting matched to the wrong treatment. It is now well-documented that NSCLC patients with a driver mutation who receive an immune checkpoint inhibitor (ICI) before they receive a targeted therapy show a much higher incidence of severe immune-related adverse events that require hospitalization. This has been reported in patients with EGFR mutations receiving osimertinib after an ICI³³ and in patients with oncogenic alterations in ALK, ROS1, or MET receiving crizotinib after an ICI.³⁴

Recommendation: To appropriately integrate the use of diagnostics into the ICER Value Assessment Framework, we recommend ICER provide guidance on the standards that diagnostic tests should meet in order to be incorporated into an evaluation of a therapy, or at a minimum provide information on the clinical and analytical validity of the diagnostics that were used for the therapy selection in the ICER model.

F. Allow flexibility in the calculation of budget impact in the Value Assessment Framework

Budget impact (a population-level measure) is not a measure of whether a treatment is of good value or not. While the median age of a lung cancer diagnosis is 70 years,¹ there is a significant and growing population of younger patients. In this younger patient population, there is a 59% increased chance of detecting a targetable alteration, as compared to patients above the age of 50.³⁵ Compared to traditional chemotherapies, targeted therapies provide a far superior survival profile with fewer side effects. Therefore, use of these targeted drugs will determine whether the population of young lung cancer patients is healthy enough to resume employment and reclaim years of economic productivity. The budget impact analysis conducted by ICER is unlikely to capture these complex nuances of lung cancer epidemiology and treatment (along with patient preferences and disease heterogeneity as described above). While the Department of Labor has not analyzed these statistics, as this population of younger lung cancer patients continues to grow, the true economic impact of a lung cancer diagnosis on this younger population will become evident. Furthermore, ICER's current methodology of budget impact analysis relies on threshold calculations that not only erroneously inflate the budget impact of lung cancer precision therapeutics but also underestimate the value component of these drugs.

Recommendation: We strongly urge that ICER make their model publicly available and not use the ICER-calculated \$815 million/per drug threshold criterion. This will enable stakeholders to utilize their



own criteria of price, uptake, and time horizon, and derive their own budget impact. In addition, we recommend that ICER continue to iterate on its existing model as data on the epidemiology and genetics of the younger lung cancer population continue to evolve.

Conclusion

We urge the audience and users of ICER models to recognize that the Value Framework is static and estimates the price of a treatment at a singular point in time based on clinical trial data, a best-case situation analysis of access of diagnostics and therapeutics, and mathematical assumptions. The framework needs to be contextualized with the clinical reality of patients, such as clinical and patient heterogeneity of lung cancer and the line of treatment a patient is receiving.

LUNGEvity sincerely thanks you for the opportunity to comment on ICER's Value Assessment Framework and offer suggestions on how to improve its accuracy and to reflect the patient voice. 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 framework.

As stated, the areas of concern that we have outlined above can be actively discussed with my staff, me, 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 aeferis@lungevity.org if you have any questions or would like to engage in further dialogue.

Thank you for your attention to this very important matter.

Sincerely,

A handwritten signature in black ink, appearing to read "Andrea Stern Ferris".

Andrea Stern Ferris
President and Chairman
LUNGEvity Foundation

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October 18, 2019

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

Re: 2020 Value Assessment Framework: Proposed Changes

Dear Dr. Pearson,

The Muscular Dystrophy Association (MDA) thanks the Institute for Clinical and Economic Review (ICER or the Institute) for the opportunity to comment on ICER's "2020 Value Assessment Framework: Proposed Changes."

MDA is the nation's leading nonprofit organization dedicated to transforming the lives of individuals living with muscular dystrophy, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA) and other neuromuscular diseases (NMDs) through innovations in science and innovations in care. MDA fulfills its mission by funding biomedical research, providing access to expert clinical care and support through its national MDA Care Center Network which is comprised of expert medical clinics at more than 150 of the top health care institutions across the US, and by championing public policies and programs that benefit those it serves. Since inception, MDA has funded more than \$1 billion in research grants to accelerate treatments and cures for neuromuscular disorders, making MDA the largest source of neuromuscular disease funding in the U.S. outside of the federal government.

As of October 2018, 275 clinical trials for over 190 potential therapies were ongoing for the neuromuscular community, including for many therapies that could be the first FDA-approved treatments for their populations. As a result, MDA expects that ICER will conduct multiple reviews for NMD therapies under the proposed updated framework in the year 2020 and beyond.

Consequently, MDA is pleased to provide comments on ICER's updated framework and the proposed revisions within. We appreciate several of ICER's proposed revisions pertaining to the use and collection of real-world evidence, alternatives to quality-adjusted life years (QALYs), discussion of additional benefits to families, caregivers, and employment, and more robust stakeholder and patient organization engagement. However, we remain concerned with the quantitative exclusion of many non-traditional elements of value of importance to the NMD community, as well as revisions to the cost effectiveness thresholds for ultra-rare therapies.

Real-World Evidence:

MDA supports ICER's intent to expand its efforts to integrate real-world evidence (RWE) into its assessments. We are particularly supportive of ICER's intention to proactively collect real-world evidence in partnership with stakeholder organizations if no such evidence has already been collected.

As ICER recognizes, real-world evidence supplements data collected through clinical trials to further capture the lived experiences of patients with the disease or therapy in question. Clinical trials often offer only a limited snapshot on the safety and effectiveness of a therapy as inclusion/exclusion criteria limit the patient population from which data is captured, and only certain endpoints are included. This naturally leaves many patient experiences unexplored and unempirically investigated.

Real-world evidence collected by stakeholder organizations can help fill this gap, particularly in rare neuromuscular diseases that are still often misunderstood. MDA is collecting this data for the NMD community through our neuroMuscular ObserVational Research (MOVR) Data Hub. MOVR, launched in 2018, captures clinician-reported real-world evidence at locations throughout our network of over 150 clinical care centers. Currently we are capturing data for patients diagnosed with several neuromuscular diseases, including SMA, ALS, and Duchenne and Becker muscular dystrophy and we plan to expand this list as MOVR is implemented in more locations across the country.

We are pleased that ICER is committed to not only more extensively include RWE within its assessments but also to partner with stakeholders to collect RWE when otherwise unavailable. This will be particularly important for rare disease assessments where data and disease understanding are limited, and resources to collect such data are limited. We strongly encourage ICER to proactively and deliberately partner with patient organizations to collect such data necessary to fully understand the potential impacts of a new therapy.

Finally, MDA asks that ICER pause or delay the start of any review if data is missing that could enhance understanding of the safety and effectiveness of a new therapy. For example, RWE could be highly instructive on the potential benefits of new therapies for Duchenne muscular dystrophy (as well as many other NMDs), but such data, as of now, is not commonly collected. Within DMD, the six-minute walk test has been the most widely used endpoint even many patient advocates contend it poorly captures function that is important to patients. Instead, other endpoints pertaining to arm movements, lung and heart strength, and compensatory movements hold much more promise, and could be collected as RWE. In such a circumstance, rather than moving forward and concluding a review of new therapies in Duchenne muscular dystrophy (DMD) without salient RWE in hand, we ask that ICER delay such a review and collect instructive RWE to better inform any conclusion ICER may reach.

Alternatives to Quality Adjusted Life Years (QALYs)

MDA supports ICER's efforts to consider alternative measures of health improvement other than the QALY. We acknowledge and understand that many believe the QALY discriminates against

those with disabilities, and we agree that alternative measures of health improvement should be considered to better inform coverage and reimbursement decision making.

Consequently, ICER's continued use of equal value of life years gained (evLYG) as an alternative to QALYs will hopefully better inform decision makers on the implications of using the QALY in evaluating health improvements for individuals with disabilities. We urge ICER to continue to think innovatively on how best to measure health improvement outside of entrenched health economic practices.

Removal of Expanded Cost-Effectiveness Threshold for Ultra-Rare Disorders

MDA is concerned with ICER's proposal to apply uniform cost-effectiveness thresholds of \$50,000, \$100,000, \$150,000 and \$200,000 per QALY rather than expanding threshold estimates to \$500,000 per QALY for ultra-rare disorders as is currently practiced. Empirical evidence has shown that treatments for ultra-rare diseases receive higher societal value than those for common disorders, hence justifying the higher cost effectiveness threshold. As far as we are aware, this higher societal value or willingness-to-pay for rare disease therapies has not changed over the previous several years.

Additionally, ICER's reasoning for eliminating the higher cost-effectiveness threshold for ultra-rare disorders is troubling. Whether biopharmaceutical companies are misusing the higher levels in order to justify higher prices should be inconsequential to an empirical, quantitative evaluation supported by evidence.

We ask that ICER reconsider this proposed move towards uniformity as ultra-rare conditions, including many neuromuscular conditions, are anything but uniform in the therapeutic development challenges they bring and the unique benefits they offer to patients, families, and society more generally.

Controversies and Uncertainties Section

To reiterate comments submitted to ICER on its proposed framework for SSTs,

“MDA supports the addition of a section to identify uncertainties as ignoring them would result in an incomplete evaluation. However, we caution against the use of the word “controversies” within the title of the section. There will be uncertainties in economic reviews, and within those uncertainties there may be diverging views and perspectives, but divergent thinking and analysis does not necessarily result in controversy.

Within this section, we support ICER's intention to discuss alternative model structures submitted by outside stakeholders and would urge that any considerations and/or modeling that is proposed by outside stakeholders be published and responded to in finalized recommendations by ICER. Knowing the source of outside counsel is essential in the community evaluation of the recommendation, and transparency will be essential in such valuation exercises. We encourage ICER to remain open to alternative ways of

measuring the value of SSTs. By allowing for outside submissions, ICER will create a more inclusive process.”

Additional Contextual Benefits and Considerations

MDA supports the additional inclusion of contextual benefits and considerations for family members, caregivers, and the ability to find employment. Each new therapy for neuromuscular diseases has the potential to substantially benefit family members and caregivers. Patients may be able to be more independent, allowing family and caregivers to work or pursue other passions. Additionally, seeing a loved one maintain their health, or even regain health previously lost, can be incredibly rewarding to family. In addition to familial benefits of new therapies, any therapy that maintains or improves the ability of the individual to work can have substantial beneficial impacts on the patient and their family. Finding employment not only facilitates self-sustainability but increases access to needed benefits and provides psychological rewards to those who desire to find employment.

While we are pleased that these additional benefits will be considered qualitatively by the independent voting committees, the continued quantitative exclusion of these benefits remains concerning. The quantitative exclusion of elements of value important to patients, such as the value of hope, scientific spillover effects, and insurance value, allows such values to be easily ignored by decision makers. To reiterate sections of MDA’s comments on ICER’s SST framework:

“Value of Hope: ICER appears to misunderstand the “value of hope” in a way that allows the Institute to exclude this important value from its evaluations. ICER defines the “value of hope” to be the “value of having the *choice* among treatments with a different balance and timing of risks and benefits.” MDA disagrees with this alternative definition. The “value of hope” is about the potential for a more healthy and happy life in the future than was previously expected. SSTs offer patients the possibility of substantially healthier lives many years into the future, and with this brings the hope of attending college, getting married, and other important life experiences. ICER’s alternative definition ignores the hope for experiencing these seminal moments entirely.

Insurance Value: The exclusion of insurance value is concerning to MDA. ICER acknowledges that insurance value has been empirically measured by Lakdawalla et al. and through “explicit mathematical models of consumer utility maximization.”¹ However, ICER dismisses these empirical values of SSTs by stating that insurance value, “overlaps significantly with considerations given to severity or burden of illness.” We disagree; there is not enough overlap between insurance value and burden of illness to justify excluding insurance value. Burden of illness studies pertain mostly to those directly affected by the disease while insurance value pertains to those not yet affected. Insurance value, as ICER acknowledges, is about peace of mind for individuals

¹ 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):131-139.

who do not have the disease, and therefore such values are not captured within burden of illness values.

Additionally, ICER's assertion that including insurance value within its assessments in an empirical manner would result in too substantial of an impact is discouraging. If one takes this argument to its conclusion, it can safely be assumed that all substantial values of new therapies would need to be discarded due to their financial impact, and only values that fit within ICER's vision for appropriate spending levels should be included. We view this as an incredibly subjective method for approaching value assessments.

Scientific Spillover Effects: ICER's exclusion of empirical values pertaining to scientific spillover effects is subjective and serves to skew its value assessments. ICER again acknowledges that scientific spillover effects have been empirically measured but disregards such values as duplicitous with the value the future therapies will derive, and problematic due to the opportunity costs they will create for other patients.

MDA is concerned by ICER's stance on behalf of unnamed patients that including alternative values of therapies will present opportunity costs for other patients in the healthcare system. This argument can be used for any value anywhere within our healthcare system, (or our society in general), but ICER is only applying this concern to these additional elements of value.

In general, MDA is disappointed that ICER appears to be subjectively picking and choosing which empirical values it includes within its assessments based upon opinion and insufficient reasoning. We request that ICER reconsider excluding these empirical values."

MDA requests once more that ICER continue to explore empirical methods to include nontraditional elements of value to patients not captured by the QALY or evLYG. Without these values, patients and their advocates will continue to view ICER evaluations as incomplete and an inaccurate capture of the value derived from these therapies.

Potential Exclusion from Future Therapies:

To once again reiterate MDA's comments to ICER's framework on SSTs,

"MDA is supportive of ICER's intention to include considerations of the implication of SSTs potentially excluding patients from being able to take future SSTs due to the mechanism of action or immune response. We are aware that certain disease modifying therapies, particularly gene therapies and gene editing technologies, provide irreversible effects. These therapies may also disqualify patients from future ability to take other SSTs or disease modifying therapy.

This is a very real issue that patients today must grapple with. Including this possibility in an empirical manner within ICER's assessments is appropriate. However, including this potential harm of an SST while excluding many potential unique benefits is troubling. If

ICER is to include the potential unique harms of SSTs, it must also include the potential unique benefits.

However, we again wish to reiterate that this should not be the only unique benefit, or in this case disadvantage, of SSTs considered by ICER. There are many additional unique benefits that SSTs can offer to patients that ICER has chosen to exclude. We encourage ICER to assess our comments on the proposed SST framework for our fully elucidated perspective.

Stakeholder Engagement

MDA is broadly supportive of the proposed changes to methods of stakeholder engagement with patient organizations included within the proposal. We are pleased that ICER is expanding its interaction with patient organizations by conducting earlier outreach with the patient organizations representing patients affected by an upcoming review. We support ICER holding debrief calls with patient organizations at the conclusion of a review, as well as expanding the opportunity to submit written comments to ICER in conjunction with independent review committee hearings.

We also support ICER's proposed changes to its reports to broaden and further emphasize patient viewpoints submitted and considered by ICER. This includes adding a "patient insights" chapter in each report and expanding the "stakeholder input" section of each report to include further discussion of what was received and considered by ICER.

We still request that ICER give additional considerations to the time and resource burdens ICER reviews place on patient organizations, particularly small, under-resourced rare disease patient organizations, as it asks for assistance and partnership with these organizations. Engaging in a meaningful way in ICER reviews can be incredibly labor and resource intensive for any organization regardless of its size, and anything ICER can do to extend participation timelines or assist patient organizations in participatory opportunities would be appreciated. ICER is already proposing to do so in a limited fashion by extending the draft report public comment period by one week, but we encourage ICER to look at other similar extensions as well.

We again thank ICER for the opportunity to comment and look forward to continuing to work with the Institute to ensure clinical and economic evaluations of transformative therapies are thorough, accurate, and beneficial and inclusive to the neuromuscular disease community. For questions regarding MDA or the above comments, please contact advocacy@mdausa.org.

Sincerely,

A handwritten signature in blue ink, appearing to read 'Paul Melmeyer', with a stylized, flowing script.

Paul Melmeyer, MPP
Director of Regulatory Affairs

October 18, 2019

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

RE: Proposed 2020 ICER Value Framework Updates

Dear Dr. Pearson:

Merck & Co., Inc. appreciates the opportunity to provide comments on the proposed updates to the 2020 ICER Value Assessment Framework. On June 10, 2019, we sent a letter to ICER providing our initial thoughts and suggestions during your public input seeking period. In this letter, we would like to offer additional comments regarding the framework updates, particularly addressing the document ICER posted on August 21, 2019:

- **ICER's new report update process**

We appreciate ICER's intention to keep its review updated. ICER currently proposes to reassess new evidence on a yearly basis to determine if a report update is needed and will issue a public statement describing next steps. We suggest ICER alert manufacturers ahead and ask for input prior to issuing the public statement. In addition to the yearly assessments, we believe ICER should also establish a mechanism to allow manufacturers to alert ICER when significant new evidence emerges that warrants an immediate report update.

It is important to incorporate high quality and relevant RWE into the report update process to confirm what was found in RCTs as well as to provide insight into potential benefits and risks that were either not explored and could not be explored in RCTs. We suggest ICER provide detailed guidance on how RWE will be evaluated and incorporated in its review process.

- **ICER's new evidence rating system**

ICER proposes to expand evidence rating categories, aiming to "more effectively distinguish between situations that may share a high certainty of at least a comparative net health benefit but have the potential for widely different best-case scenarios." However, we do not believe the newly proposed evidence rating system will help ICER achieve the goal. Previously, we suggested ICER revamp its overly complicated, difficult-to-interpret evidence rating scales. The currently proposed rating system is just as complicated, and difficult to interpret, as the one it intends to replace. We suggest ICER use a more straight-forward evidence rating system such as GRADE that has been widely adopted by international HTA groups.

- **Crosswalk between ICER and German HTA evidence ratings**

For each future review, ICER proposes to provide a crosswalk between its own evidence ratings and those of the German HTA system. While we understand ICER wants to make its reviews more informative for non-US users, we are concerned that reporting two sets of evidence rating in the same report may cause some confusion among both US and non-US users. The German HTA system does not fit to the US context. We believe ICER should devote more effort to understanding the values and perspectives of Americans and less time trying to adapt systems in other countries to the US health care system.

- **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).

- **ICER's model transparency program**

We appreciate ICER's effort to make the modelling process more transparent. However, the current ICER model transparency program is still insufficient. We believe ICER should further improve the program to allow manufacturers to have more opportunities and time to review models and provide therapeutic area expertise prior to release of draft reports. We also suggest ICER include an industry model as part of the review process. This approach has approved effective in the ACIP evidence review process.

Again, we appreciate the opportunity to provide comments on the 2020 ICER value framework updates. We look forward to continuing the dialogue with ICER regarding value assessment.

Sincerely,



Fang Sun, M.D., Ph.D.
Director, Medical Policy, HTA & Value Assessment
The Center for Observational and Real-World Evidence (CORE)
Merck & Company, Inc.

Submitted Via Email: publiccomments@icer-review.org

October 18, 2019

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

RE: 2020 Value Assessment Framework Proposed Changes

Dear Dr. Pearson:

Mallinckrodt Pharmaceuticals (“Mallinckrodt” or “the Company”) appreciates the opportunity to provide feedback on the Institute for Clinical and Economic Review (ICER)’s “2020 Value Assessment Framework Proposed Changes,”¹ as released on August 21, 2019.

Mallinckrodt is a global business that develops, manufactures, markets, and distributes specialty pharmaceutical products and therapies. Areas of our Specialty Brands business focus include autoimmune and rare diseases in areas such as neurology, rheumatology, nephrology, pulmonology, and ophthalmology; immunology and neonatal respiratory critical care therapies; and gastrointestinal products. To learn more please visit: www.mallinckrodt.com.

Mallinckrodt is pleased to provide comments on selected areas of ICER’s value assessment framework for proposed revisions for 2020 and beyond. Our comments focus on the following areas:

Comparative Clinical Effectiveness

- **Section 3.1 Sources of Evidence:** We appreciate ICER’s reaffirmation of the use of real-world evidence (RWE) and the recognition that RWE may complement other evidence, through providing additional information on comparative clinical effectiveness and other benefits of an intervention. We further appreciate ICER’s commitment to partnering with organizations that may serve as sources of RWE during reviews, and strongly recommend further collaboration with patient organizations and others around use of RWE.
- **Section 3.3 Cross-Reference with German Evidence Ratings:** We are concerned with ICER’s proposal to translate its judgments of evidence into the system used in Germany

¹ Institute for Clinical and Economic Review. 2020 Value Assessment Framework Proposed Changes, August 21, 2019. Available at: https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_VAF_Proposals_082119-1.pdf

given the significant differences between Germany's HTA process and ICER's value assessment framework.

Long-Term Cost Effectiveness

- **Section 3.1 Measures of Health Gain:** While we appreciate ICER's acknowledgment of some of the challenges of the use of the Quality Adjusted Life Year (QALY) through the development of the equal value of life year gained (evLYG) measure, we believe more should be done to address and acknowledge the limitations of the QALY.
- **Section 3.2 Quantifying Additional Dimensions of Value:** While we understand that there are challenges in quantifying value that fall beyond the scope of traditional methodologies for value assessment, we urge ICER to continue to consider the inclusion of such metrics, as they are instrumental components of capturing value to patients.
- **Section 3.6 Alternative Economic Model Assumptions:** While we appreciate acknowledgement of alternatives to the ICER value framework that may be suggested by stakeholders, we believe that such alternatives should be more fully incorporated into the value assessment, rather than placed in a "Controversies and Uncertainties" section of the assessment report.

Potential Other Benefits or Disadvantages and Contextual Considerations

- **Section 4.1 List of Voting Questions and Voting Format:** We appreciate ICER's proposed changes to ensure better clarity and consistency in the voting process, and to make considerations for certain treatment advantages in balancing risks and benefits or that can help improve patient adherence. We are concerned, however, with ICER's movement to a single "health loss" contextual consideration, as we believe the previous measures of "severity of illness" and "lifetime burden of illness" are unique and should be considered separately for purposes of the voting process.

Report Development and Public Meetings

- **Section 6.1 Report Development – Process to Reassess New Evidence:** We appreciate ICER's proposal to reassess whether new evidence has emerged that should be included in a public report. We encourage ICER to broaden the timeline for consideration of new evidence and to incorporate greater stakeholder input into the process.
- **Section 6.1 Report Development – Changes to the Public Comment Process:** We appreciate ICER's adaptations to the public comment period for class reviews and to word limits for summaries of oral comments. We further believe that ICER's processes for value assessment could benefit from greater transparency.

- **Section 6.1 Report Development – Patient Perspectives:** We appreciate ICER’s creation of a new chapter report that describes input received from the patient community. We continue to encourage ICER to better incorporate patient perspectives into the actual value assessment determination.
- **Section 6.1 Report Development – Relationship of Value Assessments to Product Approval by the Food and Drug Administration (FDA) Approval Date:** We ask ICER to ensure that value assessments are not conducted prior to a drug’s approval by the FDA. This will ensure that necessary information, including a robust assessment of benefit/risk, is fully available should an assessment be conducted.

Stakeholder Engagement

- **Stakeholder Engagement, Section 7.1:** We appreciate ICER’s steps to make more information available on how patient inputs have been used in a value assessment report and to formalize the practice of debriefing with patient organizations following a review. We continue to encourage ICER to work more collaboratively with the patient community to inform value assessment outcomes.

Further comments in each of these areas are detailed below, organized by section in the document.

* * *

1. Comparative Clinical Effectiveness, Section 3.1 Sources of Evidence

Mallinckrodt appreciates ICER’s commitment to seek and use existing RWE in its reviews. RWE can play a critical role in the development and approval of new treatment innovations for patients. RWE and observational studies also provide important details around the impacts of a treatment intervention for patient health outcomes. As such, we believe the incorporation of RWE can improve ICER’s value assessments and overall determination of net health benefit. We were disappointed to see narrow use of observational studies in ICER’s recent Unsupported Price Increase Assessment Report.² In this review, ICER excluded a number of observational studies based on the scope of the comparison as it related to price increases, limited information on study design, study comparator arms using the same drug, or not meeting ICER’s criteria for assessing efficacy.³ We believe observational studies can provide critical RWE on product use in patients, and we urge ICER to broaden its consideration of such studies in future assessments and reports. While we recognize that there are still uncertainties and potential limitations to the use of RWE, there are similarly limitations to comparative effectiveness and value assessment processes, as demonstrated by continued enhancements to ICER’s framework. As such, we

² Institute for Clinical and Economic Review. Unsupported Price Increase Report, 2019 Assessment. October 8, 2019. Available at: https://icer-review.org/wp-content/uploads/2019/01/ICER_UPI_Final_Report_and_Assessment_100819_Final.pdf.

³ *Id.*

support ICER's continued consideration of RWE in the value assessment process, and encourage inclusion of such data and evidence in determinations of value.

The draft framework notes that ICER will “explore collaborative relationships with organizations that may serve as sources of real-world data...” As ICER develops these collaborative relationships, we encourage ICER to also promote strong engagement with stakeholders in the collection and use of real world data and RWE. As recognized by the Bipartisan Policy Center's paper on expanding the use of RWE, collaboration among regulators, payers, clinicians, patients, and other key stakeholders is needed to leverage this transformational information sharing.⁴ In particular, patient organizations can play a critical role in the collection and generation of patient outcomes and RWE data. We believe that as ICER engages the patient community, they should seek out opportunities to work with patient organizations to collect and factor such data into their value assessment process.

2. Comparative Clinical Effectiveness, Section 3.3 Cross-Reference with German Evidence Ratings

In this latest update, ICER proposes to translate its judgment of the evidence rating system for added clinical benefit used in Germany. This proposal raises concern due to the fundamental differences in these two systems. Further, we are concerned about offering a secondary rating system. Contrary to offering a differing way for decision makers to consider the strength of evidence supporting new interventions, we believe this will only create further uncertainty and confusion, all while ICER seeks to enhance its value framework for the future.

3. Long-Term Cost Effectiveness, Section 3.1 Measures of Health Gain⁵

While ICER proposes no specific changes to this section, Mallinckrodt remains concerned with the foundational use of the Quality-Adjusted Life Year (QALY) as the underlying metric for value assessments. While we appreciate ICER's acknowledgement of some of these concerns through the development of the equal value of life year gained (evLYG) measure, we believe more could be done to address the use of QALYs and their specific limitations as it relates to valuing treatment across patient populations.

For example, the recent International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Special Task Force on Value Frameworks Report highlights several elements of value that may not be adequately captured by the standard QALY, including: (1) reduction in uncertainty; (2) fear contagion; (3) insurance value; (4) severity of disease; (5) value of hope; (6) real option value; (7) equity; and (8) scientific spillover.⁶ Further, although widely used by

⁴ Bipartisan Policy Center. Expanding the Use of Real-World Evidence in Regulatory and Value-Based Payment Decision-Making for Drugs and Biologics. August 2019. Available at: https://bipartisanpolicy.org/wp-content/uploads/2019/08/Health_Innovation_Real-World_Evidence_Report_R04.pdf.

⁵ We note that there are two sections 3 in the proposed framework.

⁶ 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. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(2):131-139.

HTA agencies, the QALY has significant limitations including ethical considerations, methodological issues and theoretical assumptions, and context or disease specific considerations.⁷ Other limitations with the metric have also been identified, relating to time factors, utility factors, and algorithm variation. Operationally, measuring quality of life or utility (one of the two components of QALY) is a challenging process as numerous direct and indirect methods exist. As we previously highlighted in our September 2017 comments on ICER's proposed adaptations to its value assessment framework for the assessment of treatments for ultra-rare conditions,⁸ these specific issues include:

- The QALY cannot be derived for some of the most vulnerable populations, including very young, very old or very sick populations;
- Patients with lower QALY scores whose lives are extended will have higher overall cost;
- The QALY inputs are based on clinical evidence which is hard to come by for small populations of orphan diseases;
- The QALY cannot adequately capture comprehensive value, such as important patient, caregiver, and societal benefits;
- The QALY does not holistically assess value to an individual patient;
- The QALY shortchanges the impact of innovative medicines on individual patients; and
- The QALY cannot address heterogeneity in treatment options.

We strongly urge ICER to further address the issues with the QALY as it reconsiders updates to the framework for 2020 and beyond. In order to continue to appropriately address the fact that value assessment is an evolving field, it would be helpful if these inherent challenges were acknowledged in ICER's report process, particularly as they relate to valuation of products to treat rare diseases.

4. Long-Term Cost Effectiveness, Section 3.2 Quantifying Additional Dimensions of Value

While we appreciate the proposal to incorporate additional dimensions of value into the voting process for "single or short-term transformative therapies" ("SSTs"), we believe that more can and should be done to appropriately capture a therapy's value beyond the traditional bounds of value assessment across the scope of the framework. As detailed above, the ISPOR Special Task Force on Value Frameworks Report details eight additional elements of value that are not adequately captured in existing value assessment methodologies.⁹ While we recognize that quantification of these elements can present a challenge depending on the product under assessment, we encourage ICER to consider how to better incorporate these elements of value

⁷ Pettitt DA, Raza S, Naughton B, Roscoe A, Ramakrishnan A, et al. (2016) The Limitations of QALY: A Literature Review. *J Stem Cell Res Ther* 6: 334; Nord E, Daniels N, Kamlet M. QALYs: some challenges. *Value Health*. 2009 Mar;12 Suppl 1:S10-5. doi: 10.1111/j.1524-4733.2009.

⁸ See: Mallinckrodt Comments, RE: Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions, July 2017. Submitted to ICER on September 25, 2017.

⁹ 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. *Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2018;21(2):131-139.

into the assessment framework. Many of these additional identified elements of value are critical to capturing patient perspectives.

5. Long-Term Cost Effectiveness, Section 3.6 Alternative Economic Model Assumptions

While we believe that ICER's proposed inclusion of alternative model structures and assumptions suggested by manufacturers and stakeholders is a step in the appropriate direction for identifying gaps in the value assessment framework, we are concerned with the manner in which this information will be included in assessment reports. First, by naming this section, "Controversies and Uncertainties," the inherent implication is that other evidence and modeling submitted is in conflict with ICER's assessment. The goal, however, of seeking the submission of this alternative modeling information is meant to enhance and improve the value assessment process, and inclusion in a section entitled "Controversies and Uncertainties" could be misleading. Rather, we recommend a heading more reflective of the information contained in the section, such as "Alternative Economic Modeling Assumptions." Second, as alternative economic modeling assumptions are submitted, ICER should incorporate quantitative analyses presented into the review process, and take action to better reflect qualitative information such as patient perspectives and additional elements of value.

6. Potential Other Benefits or Disadvantages and Contextual Considerations, Section 4.1 List of Voting Questions and Voting Format

We continue to appreciate ICER's inclusion of contextual considerations as a part of the value assessment process, and the solicitation of additional benefit information and contextual considerations during the open input phase of each report. To this end, we support ICER's proposed changes to ensure better clarity and consistency in the voting process on these items, as well as to consider certain treatment advantages in balancing risks and benefits and that can help improve patient adherence. We support the movement to a Likert scale, rather than a yes/no response, for consideration of these questions by the appraisal committee. These changes can help better inform the role of contextual considerations in the value assessment process. However, we are concerned with ICER's movement to a single "health loss" contextual consideration, as we believe the previous measures of "severity of illness" and "lifetime burden of illness" are unique and should be considered separately for purposes of the voting process.

7. Report Development and Public Meetings, Section 6.1 Report Development – Process to Reassess New Evidence

Mallinckrodt appreciates ICER's acknowledgement and proposed creation of a formal process for consideration of new evidence and the potential to make updates to previously completed reports. By considering new evidence that becomes available, ICER can help ensure a more comprehensive value assessment updated with new information, particularly as the use of RWE and patient perspectives in value assessment continue to evolve and likely become more frequent. The consideration of additional data can be particularly important in the rare disease

space, where initial data may be limited, but patient outcomes and RWE data can provide substantial insights.

We believe that creating a formal process or standards for when new information will be incorporated into a value assessment is critical to increasing transparency in ICER's value assessment activities. While we appreciate that ICER will provide formal notice whether a full review will again be undertaken or not, we would also urge ICER to create an opportunity as a part of this process for stakeholders to submit additional evidence for consideration for review updates. As a part of the process, ICER could convene a public forum to discuss new evidence and to hear from the stakeholder community to ensure a comprehensive approach to value assessment. Finally, we ask ICER to consider additional time periods beyond the one year mark for inclusion of new evidence, particularly as it relates to patient outcomes and RWE data.

8. Report Development and Public Meetings, Section 6.1 Report Development – Changes to the Public Comment Process

We believe that many of the changes in this proposed update to the value assessment framework will enhance the ability of all stakeholders to provide comment to ICER and increase transparency of the process. We support ICER's one week extension of the draft report public comment period for class reviews, given their magnitude, as well as the expansion of the word limit for oral comment summaries.

As value assessment is an evolving process and iterative field, we continue to support greater transparency and stakeholder dialogue. In particular, we encourage ICER to more fully acknowledge the extent to which key data points may be missing to fully form an assessment, or when there is not agreement about a particular measurement. We encourage greater openness and transparency on the areas of uncertainty or lack of clarity. As detailed above, we continue to encourage transparency in the engagement of patient stakeholders to foster a more collaborative environment on data collection and needs, patient perspectives on value, and opportunities to enhance the value assessment process.

9. Report Development and Public Meetings, Section 6.1 Report Development – Patient Perspectives

Mallinckrodt appreciates ICER's proposal to include a new "Patient Perspectives" chapter for future reports that describes the inputs received from the patient community and related patient-generated evidence. We continue to encourage ICER to better utilize patient perspectives through more comprehensive collection and incorporation of this information in value assessments. We believe that in order to best capture the patient voice, ICER should use more robust and transparent opportunities for patient engagement throughout the review process. As with RWE data consideration, these patient perspectives should not only be summarized in ICER's assessment reports, but also incorporated into the value calculus for treatment

innovations. ICER should work closely with the broader patient community on means to incorporate these value perspectives.

In addition, we appreciate ICER's consideration of and past solicitation of comments on the modification of its value assessment framework for treatments for ultra-rare conditions.¹⁰ We continue to encourage ICER to adapt its assessment considerations to address the needs of the specific patient population to be treated. Incorporation of the patient perspectives and other benefit/contextual considerations, as well as adoption of additional assessment measures identified by key clinical or patient organizations, can help facilitate this goal for rare disease treatments.

10. Report Development and Public Meetings, Section 6.1 Report Development - Not Conducting Value Assessments of a Product Before its FDA Approval Date

Mallinckrodt believes that ICER value assessments should not occur prior to FDA approval of product. This will help ensure that the full range of evidence is available in conducting an assessment and prevent against the development of a value assessment for a product that ultimately may not be approved. Without having yet received FDA approval, key elements and information, including a final product label, will not be available at the time of an evaluation. These data and information will be necessary for a complete value assessment.

11. Stakeholder Engagement, Section 7.1 Stakeholder Engagement

We believe ICER's proposed discussion of how patient inputs inform reviews, as well as the formalization of a patient organization debriefing process following a review, are critical steps in the direction of creating greater transparency in ICER's value assessment process. As discussed above in reference to the proposed "Patient Perspectives" section of the report, we believe that ICER should engage in more robust opportunities to collaborate and collect feedback from patient organizations, and incorporate these perspectives into value assessments.

* * *

Mallinckrodt appreciates the opportunity to provide input on updates to ICER's value assessment framework for future use. We look forward to continuing to work with ICER as it considers updates and refinements to its value assessment process. Please do not hesitate to contact me at kendra.martello@mnk.com or 202-459-4145 if you have any questions or wish to discuss.

Sincerely,

Kendra Martello, JD
Executive Director, Public Policy & Corporate Social Responsibility

¹⁰ Institute for Clinical and Economic Review. 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>.



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October 18, 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

RE: Comments on Proposed Changes to ICER's 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 comments on the proposed 2020 Value Assessment Framework update. Founded in 1920, the National Health Council (NHC) brings diverse organizations together to forge consensus and drive patient-centered health policy. The NHC provides a united voice for the more than 160 million people with chronic diseases and disabilities and their family caregivers. Made up of more than 125 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.

The NHC appreciates the opportunity to comment on ICER's proposed changes to its 2020 framework. We believe that while much progress has been made in recent years, there is still significant work needed to be done to fully integrate the patient voice into value assessment.

In response to ICER's proposed value framework updates, the NHC has the following suggestions and comments to ensure the framework is truly patient centered. We note and appreciate that several proposed changes are responsive to our comments submitted on June 10, 2019. Under the general topic areas below, we also offer recommendations on how to strengthen the 2020 framework and provide specific comments on particular sections of the proposed updates.

I. Promote Meaningful Patient Engagement

Public comment periods included in the revised timeline remain insufficient to facilitate meaningful patient engagement

The proposed update outlines an extended timeline for “large class” reviews by nine weeks, but this includes only one additional week for public comment. One added week is still insufficient to promote meaningful stakeholder engagement. Tables 1 and 2 below provide an overview of recent comment periods for an Asthma “Large Class Review” and an ongoing single-intervention review.

ICER provided stakeholders with a mere 4-weeks to digest and review 132 and 148-page documents filled with complex materials, analyze it, develop comments, circulate comments to their scientific advisory boards and membership, all while potentially hiring an expert consultant for assistance. This is an impossible request for patient organizations with a small staff, limited resources, and who must juggle an ICER review with other critical, mission-related daily tasks.

Table 1. 2018 ICER Asthma “Large Class Review” Timeline

Document	Public Comment Period for Asthma Large Class Review in 2018 ¹
Asthma: Draft Scoping Document	05/15/2018 – 06/05/2018
Asthma: Draft Evidence Report • 132 pages ²	09/24/2018 – 10/22/2018

Table 2. Ongoing Type 2 Diabetes Single Intervention Review Timeline

Document	Public Comment Period for Type 2 Diabetes Review in 2019 ³
Type 2 Diabetes: Draft Scoping Document	05/02/2019 – 05/22/2019
Type 2 Diabetes: Draft Evidence Report • 148 pages ⁴	09/11/2019 – 10/08/2019

Recommendation: We feel strongly that a 90-day comment period should be provided to review all draft evidence reports – not just large-class reviews. This timeframe would bring the ICER comment period more in line with the timelines of other organizations that seek to engage the patient community, such as the Food and Drug Administration (FDA). For example, recently released FDA draft patient-focused drug development guidance provides a 90-day comment period.

Comment periods should also be extended when dates fall over holidays. For example, the already limited public comment period for the asthma large-class review coincided with the Memorial Day Weekend.

Patient-facing educational materials should be co-developed with patient organizations

As part of ICER’s commitment to facilitating effective stakeholder engagement, ICER proposes to develop a series of webinars on the principles of health technology assessment and economic modeling for a general audience. The NHC process to educate patients involved conducting a

needs assessment to identify which resources needed to be developed in this area. As a result, we created an online educational series, *In the Pursuit of Value: An Introduction to Health Economics and Value Assessment*.⁵ Our modules were developed with patient community, academic researcher, and also ICER staff input. The NHC would be happy to consider developing modules on additional topics ICER might recommend.

Recommendation: Ultimately, it is critical that any patient-facing materials or trainings are co-developed with members of the patient community.

Provide clearer guidance on what patient-submitted data has been impactful and what would be useful for patients to collect and submit

We thank ICER for being responsive to our feedback that the Patient Population, Intervention, Comparison, Outcome, Timing, and Setting (PICOTS) framework serves as a platform for gathering information from and communicating with patient groups. ICER's plan to incorporate PICOTS elements into the patient survey is a welcome first step. We also appreciate ICER's proposal to develop a new "Patient Perspectives Chapter." The decision to include this chapter at the very beginning of the report is aligned with our 2018 recommendation that "VA bodies can open a VA report by leading with patient-experience input to provide context and set the stage for interpretation of the assessment. Patient groups can work with VA bodies to develop this section."⁶

Recommendation: We recommend that this new chapter should not only include *what* information was submitted by patients, but also *how* it informed the review. This would provide important lessons learned for the patient community.

Additionally, we appreciate ICER formalizing the debriefing process with patient groups. However, the proposed update states, "ICER's practice, which has been the same for many years, is to respond to draft-report comments with this degree of detail and will continue to do so; scoping documents currently describe suggestions we have accepted under a 'Stakeholder Input' heading, and we propose to include details of why some suggestions have not been adopted." We must point out that ICER has conducted dozens of reviews over recent years, and it is impractical for patient groups to sift through past reports about unrelated diseases to identify potential insights of what was useful/not useful. Thus, we remain concerned that patient groups do not have direct, clear guidance on data will that would be helpful for them to collect.

Recommendation: We suggest that a helpful resource for patient groups would be if ICER collated these responses in one place and identified key themes of patient input that was impactful or not impactful and why. This would be instructional for tailoring patient-group input. Translating this information may also provide useful insights to ICER and the patient community regarding "lessons learned." The NHC stands ready to assist to help ensure insights and lessons learned are shared broadly with the patient community.

Patient groups have become more sophisticated regarding topics related to value assessment and will increase their knowledge over time, especially from the "lessons learned." Thus, we also recommend that full economic models are made available to patient groups upon request.

II. Promote Value Assessment Methods Advancement and Transparency

Multi-criteria decision analysis (MCDA) has evolved substantially over the past decade

The Proposed Changes document states that “in 2009-2010 ICER attempted on several occasions to use a formal MCDA process in its appraisal committee deliberations. We found, as have others, that it was very difficult for participants to identify mutually independent factors in their decision-making, much less to give weights to them.”⁷ However, MCDA methodologies have evolved significantly over the past decade. In addition to ISPOR’s two task force documents,^{8,9} the Innovation & Value Initiative and the University of Colorado’s P-Value Center are each working to advance the field.^{10,11} International health technology assessment (HTA) bodies have also successfully piloted MCDA.^{12–15} For example the Belgian Health Care Knowledge Centre (Belgium’s HTA) concluded that “the results show that the proposed MCDA is feasible and acceptable for the unmet needs commission.”¹⁵

Recommendation: Given substantial researcher- and broader stakeholder-community interest in advancing MCDA, possibly as a more transparent approach to HTA, we recommend that ICER revisit MCDA by committing to at least one MCDA pilot study over the coming year to assess the ability of MDCA to capture value elements important to patients.

Greater transparency regarding shortcomings and limitations of value assessment findings

We reiterate our recommendation that quality-adjusted life year-based approaches are insufficient for capturing value from the patient perspective. In the absence of alternative approaches, the shortcomings and caveats to conclusions and recommendations stemming from these methods must be very clearly articulated. The patient community has observed “cherry picking” on the part of value assessment report users; that is, only giving attention to final cost-per-QALY findings of a report that fit a user’s agenda and ignoring those more illustrative parts that run counter to their agenda. We acknowledge that ICER has publicly stated that these kinds of actions run counter to ICER’s intent.

Recommendation: We ask ICER to continue to be responsible in calling out such actions. We highly recommend that ICER in presenting assessment findings be extremely clear in the presentation of results and blatantly transparent regarding uncertainty and assumptions. Critical caveats around interpretation cannot be located elsewhere in a report or in other documentation. Presenting results and caveats transparently also will assist stakeholders in identifying which assessment users are “cherry picking” the recommendations they adopt or ignore.

Results from the societal “co-base case” should also be presented alongside the healthcare sector perspective analysis within an evidence report, and highlighted in press releases, report-at-a-glance documents, and other decision-maker-facing materials (e.g., JMCP commentaries).

The societal perspective should be provided as the co-base case

In indicating why ICER does not present the societal perspective as a co-base, the document states that US decision-makers are not responsible for making trade-offs that involve broader societal resources. In some instances, this is true. However, most patients are employees and their employer is providing a health insurance plan as a benefit to keep the employee and his or her family members healthy and productive. It is those plans that potentially make use of value assessment report findings in their decision-making. We would counter when an employer

funding a health insurance plan benefit has a contract with a plan does not see itself as having responsibility for keeping employees and their families healthy and productive, that employer should find a plan that does.

Similarly, ICER also states in the report with regard to committee voting that “It has always been our intention to use these votes as a way to signal to *decision-makers* that the “*right*” cost-effectiveness threshold to be applied in any individual situation should be a judgment that benefits from integration of cost-effectiveness results with an intervention’s potential other benefits (or disadvantages) and broader contextual considerations that include ethical dimensions of priority setting.”

Recommendation: We recommend that a societal perspective be presented as a co-base case to provide more than a signal regarding many of the broader contextual considerations. Providing both the societal co-base case and unambiguous caveats for interpretation alongside the findings can support users, mitigate cherry picking, and emphasize critical contextual considerations.

Transparency regarding ICER policies and approaches

ICER has long stated that for value assessments to be useful, they need to be conducted around the time of launch. However, expediting reviews before sufficient evidence to conduct an assessment, which will be used into the future, is irresponsible. For example, regarding ICER’s assessment of Zolgensma, ICER’s website notes that “An update was added to this report on May 24, 2019, to reflect the FDA label and new clinical data for Zolgensma.”¹⁶ While the updated report states that overall conclusions remain unchanged, it does raise important questions regarding how ICER determines when a sufficient amount of evidence is available to conduct an initial review, and when sufficient new evidence is available to conduct a re-review. The Proposed Changes document states that ICER wants to use the “best available evidence at the time.” However, it is uncertain how ICER determines if there is a sufficient amount of evidence at the time.

Recommendation: We recommend that ICER clearly state how it determines that sufficient evidence is available to initiate an assessment – whether for an initial assessment or “reassessment”

Expanded use of real-world evidence

We appreciate ICER stating that real-world evidence (RWE) will play a greater role in upcoming reviews. Patient-provided RWE plays an important role in providing insights into patient perspectives.

Recommendation: We encourage ICER to continue to partner with patient groups to incorporate these types of RWE, which are critical to understanding the patient perspective. We encourage ICER to continue to use RWE found in the published literature and from other reputable sources. We also encourage ICER to focus its efforts in identifying, assessing, and utilizing reputable RWE rather than generating RWE *de novo*.

Cross-over to German Evidence Ratings is a distraction from the important improvements needed

There is a tremendous amount of important work to be done to improve value assessment methods. It is unclear what the value of this experimental, unvalidated crosswalk with German Evidence Ratings would be or its potential impact on US stakeholder decision making.

Recommendation: We recommend that instead of ICER expending resources to develop a crosswalk to German Evidence Ratings, ICER refocus efforts on advancing the purpose of its value assessment framework: “to form the backbone of rigorous, transparent evidence reports that, within a broader mechanism of stakeholder and public engagement, will help the United States evolve toward a health care system that provides fair pricing, fair access, and a sustainable platform for future innovation.” For example, ICER could focus its efforts piloting an MCDA approach, advancing patient-engagement methods, or studying the impact of value assessment on payer decisions, patient access, and/or utilization management.

III. 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. 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 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

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October 18, 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 refer you back to the comments submitted in our letter dated June 10, 2019, and are pleased to submit the following additional comments.

In general, we appreciate that ICER is proposing to make a variety of improvements to incorporate more patient engagement throughout the process, including to: discuss potential review topics with patient groups earlier to give them time to prepare; have a separate chapter on patient insights early in the report; revise patient engagement materials to better equip patients and patient advocates to participate in ICER's process; and formally implement post-review debrief calls with patient advocates. We support these initiatives and ask that ICER include them in the final Value Assessment Framework. We also have a number of additional recommendations regarding further changes that ICER should implement to better incorporate patient-important outcomes and data in its process.

Understanding the Diversity of Patient Experience and What Matters Most to Patients

In our June 2019 comments, we stressed the importance of including the patient voice in value assessment and, indeed, at every stage of product development and evaluation: from identification of research topics through research design, clinical trials, long-term follow-up, health technology assessment, and payer decision-making. We noted that 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, and we encouraged ICER to include relevant metrics and data from these tools in its reviews.

We are therefore pleased that ICER has affirmed its use of real-world evidence (RWE), and that ICER has further committed to explore collaborative relationships with patient groups and other organizations that may serve as sources of RWE. Real-world evidence can yield crucial information about new treatments, as confirmed by a recent study which found that, compared with randomized-controlled trials, RWE "better reflects the actual

clinical environments in which medical interventions are used, including patient demographics, comorbidities, adherence, and concurrent treatments.”¹ In the final Value Assessment Framework, we encourage ICER to be more explicit about how and when you will work with patient groups to generate RWE, recognizing that patient groups will need adequate notice to gather information. Additional specificity and guidance is needed around the standards ICER will use to evaluate the adequacy of RWE and whether it will meet the threshold for use in the formal analysis, and not just for reporting in the context and background narrative.

Finally, ICER is proposing a more formal process to evaluate whether a review should be updated a year after an initial review. In the final document, we encourage ICER to be more explicit about how patients and patient advocates will be engaged in that process and how existing or de novo RWE will be incorporated. Ideally the primary ICER evaluation will identify areas where, if available, RWE could have been included in the modeling. This specificity would provide a framework for priority RWE collection efforts and guide patients and clinical organizations in such efforts in anticipation of the one-year review.

Incorporating Patient-Generated Evidence and Integrating Dimensions of Value not Captured by the QALY

In prior letters, we have encouraged ICER to broaden its economic models to reflect all critical elements, including patient-important outcomes: to consider societal burden and indirect burdens/costs within its base case analysis, rather than relegating these elements to the “Other Benefits or Contextual Considerations” at the end of a report. While the other changes proposed by ICER to the process to consider these additional factors are improvements, we recognize that many stakeholders do not read an entire ICER report and focus instead on the economic analysis. Moreover, a narrow analysis that does not consider patient-important outcomes will lack credibility in the patient and provider communities with whom ICER seeks to work.

We are therefore disappointed that ICER proposes to make no changes with respect to incorporating additional dimensions of value in its cost-effectiveness model. We ask ICER to reconsider its rejection of the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Special Task Force on Value Frameworks and commit to further consideration of ways to incorporate these dimensions of value into its work. We agree with ICER that, “ICER and the broader HTA community have a responsibility to educate potential users of our work about the need to embed CEA [cost-effectiveness analysis] in a broader decision-making structure that is sensitive to the benefits and disadvantages of treatments that do not feature in the outcomes of clinical trials, as well as the ethical dimensions that are always inherent in any priority-setting process.” But, we would argue that qualitative discussion of patient-important outcomes in the contextual considerations section is not enough to ensure that stakeholders pay attention to those outcomes and that the process is patient-friendly.

¹ Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of Using Real-World Data to Replicate Clinical Trial Evidence. JAMA Netw Open. Published online October 09, 2019;10(10):e1912869. doi:10.1001/jamanetworkopen.2019.12869

In our June comments, we also urged ICER to rethink how it calculates long-term value – specifically, to modify the QALY calculation by incorporating discount rates within the base case analysis so as to account for the **long-term value** of health effects in relation to costs. We are disappointed that ICER has chosen to make no change in the discount rate it uses in its modeling.

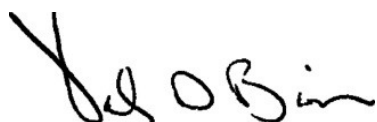
Ultra-Rare Framework

In our June comments, we reiterated our previously-raised concerns regarding ICER’s employment of a low and arbitrary threshold for defining ultra-rare conditions. We urged that additional factors (e.g., disease severity and potential for a significant gain in quality or length of life), should also be taken into consideration. We regret that ICER continues to limit its ultra-rare framework to conditions affecting fewer than 10,000 individuals.

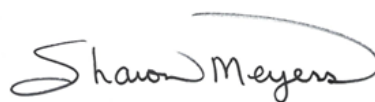
We also reiterate our request that you clarify how ICER’s different versions of its Value Assessment Frameworks might intersect. We anticipate that a review of a gene therapy treatment for hemophilia, for example, might be eligible for both the Single or Short-Term Transformative Therapies (SST) model and the ultra-rare framework. Please clarify whether and how the SST Model and ultra-rare framework would intersect if the treatment under review met both criteria.

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'.

Val Bias
Chief Executive Officer
National Hemophilia Foundation

A handwritten signature in black ink, appearing to read 'Sharon Meyers'.

Sharon Meyers, M.S., CFRE
Interim President & CEO
Hemophilia Federation of America



October 18, 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 offer feedback on the Institute for Clinical and Economic Review's (ICER) proposed changes to its 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.

We applaud ICER for seeking public input from a variety of stakeholders to inform the proposed changes to its 2020 assessment framework. As the U.S. health system evolves in its use of value assessment to inform coverage determinations, 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 believe that this data can be utilized along with other comparative effectiveness research to improve health outcomes for people in the United States.

Report Development and Public Meetings

The Society is pleased that ICER acknowledges the importance of input and engagement with patients and the patient group community and acknowledges the importance of incorporating the "patient perspective" into their reports. We are appreciative that ICER will expand its timeline for large class reviews by nine weeks. However, we believe that only extending the comment period by one week will still present a steep challenge for patients and patient groups seeking to comment on these reviews. **We believe that a minimum of 60-day comment periods should be the norm for stakeholders to review draft evidence reports. We also advise ICER to monitor when comment period dates fall over federal or religious holidays and avoid setting due dates that fall during these times.**

Patient Perspective Chapter

The Society has advised ICER to incorporate the patient perspective throughout their reviews. We urge ICER to convene calls with patient organization early and often at the beginning of the review process. These conversations should inform the background and supplement ICER's knowledge of the disease state. We then urge ICER to schedule a follow up call with these groups specifically on the proposed economic model, what elements and data are being incorporated into that model and solicit feedback from the patient groups on what data could be used to incorporate the patient perspective into the model. We remain concerned that the separation of the patient perspective from the other elements of the review fails to acknowledge the importance of that perspective on the overall determination of value for the treatments under review and continues to separate the patient perspective from the economic model. If ICER does employ a patient perspective chapter, we urge

you to use the patient perspective chapter to discuss the methods utilized to inform the patient perspective throughout the review and detail how patient perspectives informed the model.

Comparative Clinical Effectiveness

Long Term Cost Effectiveness

The Society has previously submitted comments to ICER regarding our concerns with its use of QALY in determining value for people with MS. We reiterate our call for ICER to convene a team of stakeholders in a transparent process to discuss the issues surrounding societal willingness to pay and other value perspectives that may lead to the development of a metric that includes the perspective of patients and caregivers that can be utilized in the American market. We believe the uniqueness of the American healthcare system necessitates this discussion.

Alternative Economic Model Assumptions

The Society supports the addition of the “*Controversies and Uncertainties*” section to the cost-effectiveness section of its report in order to broaden discussion of alternative model structures and assumptions suggested by manufacturers or other stakeholders. We believe that it would be beneficial to all stakeholders if ICER would share its proposed model with stakeholders – particularly with patient groups or patient representatives – in order to gain insight from this community on what data would be most useful to inform the model. This would be particularly important vis-a-vis real-world data that could address areas of controversy or uncertainty where real-world data/evidence might be needed or helpful.

In past correspondence, the Society has recommended other value perspectives that could be incorporated in the report to inform the economic model to ensure that endpoints that matter to patients are reflected in the model. These include Disability adjusted life years (DaLY), 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. ICER currently addresses many of these issues as a part of their other benefits and contextual considerations section. However, the Society remains concerned that without a way for these to be incorporated into the modeling, the full impact of what is important to the patient cannot be taken into consideration. We urge ICER to allow patient groups and other stakeholders to examine the proposed model. This level of transparency would go a long way to lessening the perceived ambiguity concerning ICER’s process and promote better discussions amongst stakeholders on areas where additional data or real-world data would be beneficial.

The addition of this process to ICER’s timeline of engagement with external stakeholders will aid with transparency around what data is/is not helpful to the model and address issues arising from the other inputs that stakeholders provide when examining cost-effectiveness in the overall discussion of value. We advise ICER to add this process as a separate step in the review timeline, and not release the draft model as a component of the draft scoping document.

Sources of Evidence

The Society was pleased to see that ICER reaffirms its commitment to utilizing real world evidence in its reviews. We believe that ICER’s reviews would benefit from incorporating evidence captured outside of a clinical trial into their economic models. We believe this data will better demonstrate the impact of treatments on the patient experience, caregiver costs and utilities, subgroup analysis

and offer insight on quality of life impacts that are not routinely captured in clinical trials. As ICER works to generate new real-world evidence in its reviews, we urge you to collaborate with patients and patient advocacy groups that may have sources of evidence that could improve the economic models. Early engagement with patient groups can show areas where data gaps exist and where real-world evidence may help address these gaps.

We urge ICER to establish best practices or pilot opportunities for stakeholders to offer guidance on what types of evidence would be most useful to the models. Further, ICER should clarify how that data should be weighted compared to the clinical trial evidence that is utilized in the review. These clarifications would help stakeholders understand the parameters around real world evidence and will raise the standard of data that is submitted to ICER for its consideration. Additionally, providing guidance on why data submitted to ICER was/was not deemed appropriate for inclusion would be equally helpful.

Potential Other Benefits and Contextual Considerations

The Society supports changes that will improve clarity, transparency and consistency of interpretation for the appraisal committee members. We believe this section of the report should serve to support the clinical evidence and marry the themes from the lived experiences of patients and caregivers to put the clinical trial data into perspective on how a treatment functions in the real-world. We are supportive of ICER's proposed changes to this section but will continue to urge ICER to work with stakeholders to have critical components of the other benefits and contextual considerations fed into the economic model as much as the data allows. We appreciate the methodologic complexity involved in this process; however, some of the elements that ICER currently classifies as "other benefits and contextual considerations" impact adherence - the risk/benefit profile of the therapy, delivery mechanism or regimen complexity- and should be addressed by or inform the economic model.

Change of Voting Structure

The Society is supportive of ICER's change from a yes/no format to a Likert scale model. We believe that this would offer more nuance in the appraisal committee's vote, particularly for areas where more data may be necessary to reach definitive conclusions. In our previous comments on the framework, we recommended 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. We still believe that this would be beneficial to fully inform the review panel and provide context to inform the discussion. Since the full breadth of evidence is not incorporated into the clinical evidence review and vote, We believe that holding the first vote on contextual considerations will more effectively keep key considerations of patients in the forefront as the committee votes on the clinical evidence that was presented. We therefore strongly urge ICER to make this change to the voting structure.

Thank you for the opportunity to share our comments on ICER's proposed updates to its 2020 value assessment framework. 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 and dialogue around the assessments of value for MS therapies.

Sincerely,

A handwritten signature in black ink, appearing to read "Bari Talente". The signature is fluid and cursive, with a long, sweeping underline.

Bari Talente, Esq.
Executive Vice President, Advocacy



October 18, 2019

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

Re: ICER Proposed Changes to 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) for the opportunity to provide comments on its 2020 Value Assessment Framework Proposed Changes (Proposed Changes).¹

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 healthcare ecosystem that addresses the needs of rare disease patients. Such an ecosystem includes accessible, high-quality care as well as the development of, and affordable access to, safe and effective orphan therapies. ICER and other similar entities play a critical role in assisting these efforts through the promotion of sustainability and the valuation of care.

A healthcare system that supports rare disease patients must promote innovation, yet it must also be sustainable. Achieving sustainability starts with being able to evaluate care and determine the appropriate corresponding investment. By analyzing the value of care through rigorous, comprehensive empirical methods, health technology assessment (HTA) provides a vital mechanism for making such determinations and helping decisionmakers navigate and shape the healthcare space.

As one of the leading HTA entities in the United States, ICER holds considerable influence over the valuation of healthcare. Consequently, the results of ICER's evaluations and the way in which ICER completes its evaluations are of great importance.

Within this context, NORD appreciates the opportunity to provide comments on ICER's Proposed Changes. NORD applauds ICER for its ongoing efforts to incorporate stakeholder feedback and consistently improve its processes. NORD remains concerned about specific aspects of ICER's reviews, though, that could result in detrimental access challenges for the rare

¹ 2020 Value Assessment Framework: Proposed Changes. (2019). *Institute for Clinical and Economic Review (ICER)*. Retrieved from <https://icer-review.org/material/2020-value-assessment-framework-proposed-changes/>

disease community in light of the aforementioned influence. The concerns NORD has with respect to the Proposed Changes are set forth below.

Use of Real-World Evidence

NORD commends ICER on its stated commitment to incorporating real-world evidence into its future reports. Pre-market clinical trials submitted as part of the Food and Drug Administration's (FDA) review process, particularly for orphan therapies, are insufficient to determine the true "value" of a product as they do not necessarily capture all of the factors that should be included in a value assessment. Clinical trials are designed to determine safety and efficacy, but those are not the only factors that compose value. The complete value of a product—to patients, their families, the healthcare system as a whole, etc.—consists of other factors, such as the ability to return to work or the reduction of caregiver burden. For example, as stated in the Proposed Changes, clinical trials may not appropriately capture the long-term benefits of a product or its durability.² Real-world evidence (RWE) is a crucial tool for the continued evaluation of products as it enables the review of data on the impact and performance of such products after they are on the market. NORD stands ready to assist ICER in its efforts to incorporate RWE in a robust manner and encourages ICER to move expeditiously in this effort to test new approaches.

Measures of Health Gain

ICER has repeatedly stated that the quality-adjusted life-year (QALY) is the gold standard of HTA, while other forms of analysis, such as multicriteria decision analysis (MCDA), are largely experimental.³ Moreover, ICER has posited that methods for implementing MCDA specifically are too inconsistent and complicated to be used in value assessment.⁴

MCDA has gained acceptance among economists, however, due to concerns over the limitations of QALY models and strict cost-effectiveness analysis (CEA).⁵ Many countries, including the United States, have eschewed the QALY as a result of moral and empirical concerns.⁶ QALY models, with their lack of sensitivity and limited measure of value, have the capacity to give certain classes of drugs an advantage over others. More specifically, by predominately focusing on the number of years added to a patient's life, the QALY puts therapies that bring alternative benefits, such as decreased nausea or an ability to sleep through the night, at a disadvantage. Fundamentally, these dilemmas stem from the fact that the QALY model currently used by ICER is unable to adequately incorporate patients' perspectives on value. MCDA, on the other hand, can incorporate several additional measures of value, including, most importantly, the patient perspective.

There may be valid concerns regarding the implementation of MCDA, but that does not negate the need for the voice of the patient to be included in the quantitative assessment that is

² 2020 Value Assessment Framework: Proposed Changes. (2019). *Institute for Clinical and Economic Review (ICER)*, 5. Retrieved from <https://icer-review.org/material/2020-value-assessment-framework-proposed-changes/>

³ Ibid. Pgs. 11, 13

⁴ Ibid. Pg. 33

⁵ See, e.g., Weighing Cost-Effectiveness Analysis and MCDA as Future Decision-Making Methodologies. (2019). *Journal of Clinical Pathways*. Retrieved from <https://www.journalofclinicalpathways.com/news/weighing-cost-effectiveness-analysis-and-mcda-future-decision-making-methodologies>

⁶ ECHOUTCOME. Final Report Summary. 2013. Retrieved from <https://cordis.europa.eu/project/rcn/94071/reporting/en>

ultimately used to determine access to care. ICER's current QALY model does not adequately capture the views of patients, particularly patients living with rare diseases. There are many challenges associated with incorporating additional dimensions of value, but the inclusion of these values, particularly the patient perspective, is paramount.

NORD appreciates ICER's efforts to lift up the patient voice, such as in the most recent proposal to add a standalone chapter on the patient perspective. Relegating the experiences of patients to purely qualitative considerations, however, is simply not enough. The unfortunate reality is that, contrary to ICER's desires, far too many payers and other key decision-makers are not "embed[ding] CEA in a broader decision-making structure," but instead pointing to ICER's CEA as justification for creating barriers to access.⁷ Consequently, NORD urges ICER to revisit its deliberation on alternative measures and to strongly consider adopting methodology that allows for quantitative inclusion of patient input and recognizes disease heterogeneity. As a part of these efforts, NORD encourages ICER to continue to proactively engage stakeholders, including economists of varying viewpoints, to discuss additional paths forward.

Cost-Effectiveness Threshold Ranges

ICER previously created a discrete and higher cost-effectiveness threshold range for orphan therapies in order "[t]o address the distinctive nature of decision-making for these treatments."⁸ As ICER acknowledges, there are complexities that are raised when employing different thresholds, including the ethical issues associated with prioritizing certain categories of patients over others. Such concerns cannot and should not be dismissed. However, NORD believes that the challenges of the rare disease community are unique enough to deserve a higher range, if there is to be CEA of these therapies at all.

The Proposed Changes would reverse this policy.⁹ In justifying its decision to reverse this policy, ICER now claims that "there remain important equity concerns related to extending the threshold range higher for treatments just because they treat a small population."¹⁰ The citation associated with this statement refers to a study completed in the United Kingdom that looks at societal preferences pertaining to the allocation of healthcare resources. The study ultimately finds that there is not a preference for rare diseases, but the study also finds that there were preferences for "severity of disease, diseases for which no other available treatments exist (representing unmet needs) and medicines that reduce reliance on informal carers."¹¹ These are all characteristics that are commonplace among rare diseases. Therefore, while the basis for societal preference may not be a result of prevalence, rare diseases represent a strong surrogate measure for the factors that are determined in this study to be driving societal preference. Societal preference is a key element in supporting willingness-to-pay and subsequent cost-effectiveness thresholds. Thus,

⁷ 2020 Value Assessment Framework: Proposed Changes. (2019). *Institute for Clinical and Economic Review (ICER)*, 16. Retrieved from <https://icer-review.org/material/2020-value-assessment-framework-proposed-changes/>

⁸ Modifications to the ICER Value Assessment Framework for Treatments for Ultra-Rare Diseases: Final Version. (2017). *Institute for Clinical and Economic Review (ICER)*, 8.

⁹ 2020 Value Assessment Framework: Proposed Changes. (2019). *Institute for Clinical and Economic Review (ICER)*, 15. Retrieved from <https://icer-review.org/material/2020-value-assessment-framework-proposed-changes/>

¹⁰ Ibid.

¹¹ Linley, W. G., & Hughes, D. A. (2012). 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 Economics*, 22(8), 948–964. doi: 10.1002/hec.2872

this study actually seems to lend credence to the existence of a high cost-effectiveness threshold for orphan therapies.

ICER further states in its justification that the current economic landscape no longer supports the argument that higher prices are necessary for orphan therapies in order to sustain innovation. While this may be the case for some manufacturers, on the whole, the brief explanation provided in the report indicating that all one needs is “\$100,000 per treatment course, multiplied by a mere 10,000 patients” is misleading in its oversimplification.¹² Namely, this thought exercise is insufficient evidence to support the notion that certain pricing is no longer required to sustain innovation in the rare disease space. Small patient populations and complex science makes rare disease drug development a difficult and risky venture. Nothing has changed so significantly in the past several years as to make continued investment an easy lift.

NORD disagrees with ICER’s reversal of the essential recognition of the complexities involved in evaluating therapies for rare diseases. NORD strongly encourages ICER to reinstate the expanded threshold and apply it to all rare diseases, not just those that affect fewer than 10,000 individuals, in any future reviews.

Report Development

ICER’s reports are often issued almost simultaneously with FDA’s approval of the therapy. This can make ICER’s initial evaluation somewhat limited because information about the drug is just beginning to take shape as it enters the market. More is discovered about the value of a drug as additional patients are treated with the therapy for long enough to determine the full range of impact. As the long-term impacts become clearer and additional research is completed, possibly even resulting in additional indications, the value of a drug continues to evolve. For these reasons, NORD supports ICER’s proposal to update its report after one year. Depending on the drug, NORD also urges ICER to consider, on a case-by-case basis, whether additional updates in years beyond the first year are necessary. In many cases, important information about new drugs is learned well after the first year.

Additionally, NORD supports ICER’s proposal to increase the word limit for written summaries of public comments from 250 to 750 words. This additional flexibility would help patients better encapsulate the entirety of their thinking and their comments.

Finally, as stated previously, NORD believes that the patient perspective chapter would be a highly beneficial addition to the report. It is particularly helpful that the chapter would precede the majority of the report in an attempt to help frame the broader context. NORD remains concerned, however, that this would not be sufficient to address the access issues that can emerge as a result of payers focusing solely on the quantitative analysis contained within the report that does not contain patient input.

Stakeholder Engagement

¹² 2020 Value Assessment Framework: Proposed Changes. (2019). *Institute for Clinical and Economic Review (ICER)*,15. Retrieved from <https://icer-review.org/material/2020-value-assessment-framework-proposed-changes/>

HTA is a complex field that can overwhelm the patient community, many of whom are not economists. NORD supports ICER's proposal to create accessible seminars and update patient engagement materials. This is a step in the right direction, and NORD hopes that that ICER will continue to seek out ways to better connect with the patient community. Throughout ICER's process, outreach to patients should be frequent and proactive. The burden cannot be solely on patient organizations to make the connection, determine what might be most helpful, and gather and interpret data. The arduous, time-consuming, and overly expedited process in which patient organizations are expected to participate in ICER assessments continues to be a concern.

In order for the patient perspective to be considered quantitatively, those data need to exist. All stakeholders, including ICER, must work to facilitate the collection and adoption of such data, and that begins by building stronger relationships with the patient community. To that end, NORD stands ready to assist ICER in ensuring patient voices are well represented.

Ultra-Rare Framework

Of the over 7,000 rare diseases, there are over 90 percent that still do not have an FDA-approved therapy. Many of these diseases are severe, impact children, and create unique challenges that stem from the general lack of knowledge about them. Rare disease patients frequently struggle to obtain a diagnosis, find appropriate specialists, and benefit from therapies actually intended to treat their disease.

ICER has recognized, in part, this unique nature of rare diseases through the creation of an ultra-rare framework that coexists with the broader value assessment framework. Though not explicitly addressed in the Proposed Changes, NORD greatly appreciates ICER's efforts to accommodate the unique situation of rare diseases in its assessments. As is stated in previous comments, however, NORD 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 as defined in current statute (any disease affecting less than 200,000 individuals in the United States).¹³

NORD looks forward to working with ICER in its efforts to foster an innovative and sustainable healthcare system. For questions regarding NORD or the above comments, please contact me at rsher@rarediseases.org or 202-588-5700.

Sincerely,



Rachel Sher
Vice President of Policy and Regulatory Affairs

¹³ 21 USC § 360bb

Novartis' Feedback on ICER's 2020 Value Framework

Novartis appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER's) Value Framework update. We made several recommendations during the input period for ICER's Value Framework that were not ultimately incorporated into the value framework update. Below, we reiterate some of those recommendations as well as additional items of concern and need for clarification.

1. *Dynamic cost-effectiveness thresholds*

- a. ICER will provide cost-per-QALY results at multiple thresholds of \$50K, \$100K, \$150K, and \$200K, which is an improvement over using only a single threshold. However, evidence in the literature suggests that society may be willing to pay more than the usual \$50,000-\$200,000 per QALY in certain cases. Braithwaite and colleagues estimated the value of a QALY in the United States in 2008 by estimating the impact of health care improvements since the start of modern medicine in 1950 and also by examining survival benefits. They estimated the range for a QALY to be \$109,000-\$297,000, suggesting that the \$200,000 ceiling used by ICER is still too low.[1] Additionally, when omitting children from the birth cohort, Braithwaite and colleagues found that the estimate decreased, suggesting that diseases that significantly impact children's lives should likely have an even higher range for a QALY threshold.
- b. Further, Novartis believes that ICER should start the range at \$100K rather than \$50K. The \$100K value of a QALY is more relevant in the US marketplace, and including the \$50K threshold seems unnecessary for policy conversations in the US. In a review of cost-effectiveness thresholds, Neumann and colleagues concluded that \$50K was likely too low of a value for a QALY in the US, though could serve as an implied lower bound.[2] The finding that \$50K was too low for cost-effectiveness evaluations in the United States held true in the Braithwaite study.[1] Given that the \$50K QALY value appears to be largely a historic artifact, Novartis recommends that ICER modernize its thinking for cost-effectiveness in the US and change the lower bound to \$100K. In fact, US payers are currently developing value-based programs that are anchored at \$100K, demonstrating that this is a reasonable benchmark.
- c. Moreover, limiting the calculation of value-based price benchmarks to the \$100K-150K still links the evaluation to this value of a QALY rather than the broader range of values ICER is considering. Novartis recommends calculating value-based price benchmarks at all values per QALY rather than just producing the single value-based price benchmark. The current cut-off ignores drugs in disease areas that have demonstrated values of a QALY greater than \$150K, such as cancer [3]. Additionally, calculating value-based price benchmarks for each threshold will offer

better and more transparent information for healthcare decision makers for coverage and reimbursement decisions, as well as providing consistency across analyses.

2. *Comprehensive budget impact*

- a. A study by Precision Health Economics and the Center for Evaluation and Risk in Health at Tufts University compared real-world data to the predictions made by ICER in six assessments.[4] The unmanaged uptake used for potential budget impact calculation exceeded real-world uptake by an average 25 fold. Therefore, unmanaged uptake calculations do not represent reality, and have been overly optimistic.
- b. ICER's assumption that 100% of the eligible population would be treated at the end of five years, or that the uptake over the five years would be 20% each year is too high and does not reflect the current US healthcare landscape. The calculations used in budget impact models are based on the average number of drugs, and does not account for true outliers. The current calculation method identifies too many risks (instead of true outliers). Alternatively, ICER could report a cumulative alarm bell for the drugs reviewed over a rolling 12 months (including real-world uptake for drugs already launched).
- c. Novartis would recommend reviewing the market uptake trends of the existing treatments included in the review, and use that as an anchor point to determine appropriate uptake assumptions that are reflective of the current US landscape.

3. *Supplementing RCT evidence with RWE*

- a. ICER reaffirms use of existing real-world evidence, and is committed to identifying opportunities to generate new RWE for incorporation into reviews. Novartis agrees that it is important to include long-term data, rather than just the short-term data collected in clinical trials, and that real world evidence is a good source of long-term data for existing treatments.
- b. There can often be a gap between efficacy as measured in a clinical trial and effectiveness as measured using real world data. This gap can be more pronounced in the case of chronic diseases where benefits have a time horizon far longer than that of a clinical trial.[5] Additionally, outside of the controlled setting of a clinical trial, adherence in the real world may be more greatly impacted by treatment administration characteristics such as mode of administration or frequency of dosage and cost constraints.[6] Being able to capture the impact of these factors with longer term real world data may be helpful in evaluating the economic value of products on market.
- c. However, Novartis cautions that real world evidence generation will not be available for the new treatment under evaluation unless ICER plans to alter the timing of its

- evaluations. This would introduce some bias if long-term data were only available for some treatments, but not others.
- d. Novartis would also strenuously emphasize the importance of any real world evidence analysis generated by ICER and a partner to be completely transparent as there are numerous ways bias can be introduced into real world evidence analyses.

4. Inclusion of contextual considerations in the calculation of value

- a. ICER has indicated they will not adopt a formal multi-criteria decision analytic (MCDA) approach. They will continue to monitor the academic and policy work in this field but do not feel that MCDA, given its procedural and conceptual limitations, offers advantages to their modified approach in which factors are voted upon but not weighted.
- b. Novartis continues to believe that proper value definition is more likely to be achieved with the inclusion of a MCDA 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, and allows for local adaptability[7]
- c. MCDA is widely used in other sectors and has become a preferred method for decision analysis in many contexts.[8] 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. The Latin American Federation of Pharmaceutical Industry (FIFARMA) has endorsed the use of MDCA for making healthcare decisions, citing its advantages over traditional cost-effectiveness or budget impact models that allow for context-specific criteria, such as the inclusion of societal preferences, epidemiological priorities, and ethical values.[9]
- d. Novartis would ask ICER to reconsider this decision for future evaluations, or perhaps pilot MCDA in a future evaluation where there may be considerable contextual considerations that should to be weighed. ISPOR has a dedicated MCDA Emerging Good Practices Task Force that has released guidance to support the design, implementation and review of an MCDA.[10, 11] A transparent MCDA tool that would enable users to change the weights assigned to various elements of value could be helpful in driving decision-making.

5. Formally structured input from patients and patient advocacy organizations

- a. ICER reaffirms their commitment to seek direct patient input. They will create a new “Patient Perspectives” chapter for reports that will describe the input they have received from patients, families, and patient organizations, as well as relevant sources of patient-generated evidence. They will also summarize relevant sources of patient-generated evidence that have been shared by patients and identified through their research process.
- b. Novartis agrees with the importance of appropriately representing the patient perspective when assessing the value of treatments. Having a better understanding of patient preferences can help highlight important aspects of treatment that should be considered either from a contextual standpoint or perhaps quantified and included in the economic analysis. For example, it has been shown that patients place a higher value on therapies that provide a chance of durable or “tail-of-the-curve” survival, whereas physicians do not.[12]
- c. Novartis would also recommend that ICER reconsider quantifying patient preferences and values for formal incorporation into the short-term and long-term value assessments. Focus groups, surveys, Delphi panels, and discrete choice experiments are just a few examples of potential approaches that can be used for formal collection and evaluation of patient, and other stakeholder, preferences. Additional real world evidence should be considered wherever it is available, even if sources are available only for a subset of agents under comparative review. The outputs of these types of studies could also be used to inform an MCDA, enabling stakeholder preferences to play a role in the evaluation of the products.

6. *Increased transparency of ICER’s models*

- a. ICER feels that their process for conducting health technology assessments provides transparency in their methods to stakeholders during each phase of a review.
- b. However, there are still some ICER decisions and approaches that remain opaque, such as the net rebate calculation provided by SSR Health as well as the underlying calculations used to model disease progression and treatment outcomes in the models. Shared models from ICER do not provide sufficient detail into the actual modeling approach and calculations to allow for quality check of the models, catching errors, or providing alternate suggestions.
- c. Additionally, the ICER model share does not occur until the feedback period, which does not provide manufacturers with sufficient time to review and prepare a response. This would be true even with a 9-week timeline as proposed in the ICER update.
- d. An alternative approach would be for the ICER process to have a stronger and more open dialogue with the academic partners building the models and the manufacturers under review, as well as other stakeholders, during the model build process itself. This may take the form of more frequent phone calls to review model build progress

- and discussions over assumptions and parameter decisions. ICER could also include submissions of manufacturer product value dossiers keeping them confidential unless manufacturer agrees for public use. 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 reduce ICER's resource investment in the reviews as the involved stakeholders could help assist the academic institutions in identifying resources, information, and literature. This process would also provide a more robust way to quality check both clinical evidence, and models by comparing structures, inputs, and results.
- e. 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 that are most relevant to current clinical practice and demonstrate the best safety/efficacy profile for patients. Specifically, selecting the least costly therapy as a comparator is not necessarily appropriate for cost-effectiveness evaluations, and may not be reflective of clinical practice.
 - f. Instead, guidelines should be established, similar to the EUNetHTA guidelines, which state that the ideal comparator is the reference treatment according to up to date high-quality clinical practice guidelines. Where there is no widely agreed upon reference comparator, there should be evidence that the comparator intervention is routinely used in clinical practice, and that it is approved for the respective clinical indication/population.[13]
 - g. ICER should construct a hierarchy for selecting an appropriate comparator, considering routine clinical practice, product characteristics such as having similar pharmacological properties or mechanism of action, approved for the same use, or having comparable dosage. Additionally, ICER should only use comparators that are indicated for the condition being evaluated, particularly if the intention is to rely on clinical trial data. The full rationale for comparator selection should also be provided for stakeholder review and input.

7. *ICER proposes to benchmark against Germany.*

- a. We would strongly encourage that ICER not pursue this comparative approach to put its evaluation in context with Germany.
- b. First, it seems like a very small step away from an international pricing index or international reference pricing. Unless ICER plans to fully detail the differences between the US and Germany health contexts as well as making appropriate quantitative adjustments, this type of comparison may be used to justify price setting not appropriate to the US market.

- c. Second, the labeled indications and doses can differ by country, which may mean that the evaluations are being conducted for different patient populations or different disease manifestations, making comparisons between evaluations inappropriate.
- d. Third, the evaluations themselves may be structured differently, such as the use of different comparators, which would also make comparing the evaluations inappropriate.[14]
- e. Lastly, the timing of the Germany evaluation is unlikely to sync with ICER timelines unless ICER plans to review treatments later in the drug lifecycle than the current approach. Typically, the final evaluation rating is not completed until 6 months after launch in Germany, then at least an additional 6 months, if not more, for price negotiations to complete in order to have pricing information for an evaluation. Currently, ICER plans its review close to market launch.

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October 18, 2019

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Re: Comments on Proposed Changes to ICER's 2020 Value Assessment Framework

Dear Dr. Pearson:

The National Patient Advocate Foundation (NPAF) is pleased to submit comments responding to ICER's 2020 value assessment framework proposed changes. This letter serves as a supplement to NPAF's earlier person-centered guidance provided to ICER in April 2017.

NPAF is committed to expanding equitable access to affordable quality care. We represent the voices of millions of adults, children and families coping with serious and chronic illnesses as the advocacy affiliate of [Patient Advocate Foundation](#) (PAF), a national 501c(3) organization that provides direct assistance and support services for patients and families confronting complex, chronic and serious illness. PAF helps reduce distressing financial and other burdens people may experience because of their medical conditions.

PAF has provided case management interventions on behalf of critically or chronically ill patients since 1996, enabling them to connect with, and maintain access to, prescribed healthcare services and medications, overcome insurance barriers, locate resources to support cost-of-living expenses while in treatment, evaluate and maintain health insurance coverage and better manage, or reduce, the out-of-pocket medical and cost of living debt and household material hardships they face. PAF provides one-on-one professional case management services, working alongside patients, their loved ones, or medical professionals and often taking the lead to resolve complex healthcare access and affordability challenges encountered in the healthcare system. Through PAF's complement of case management, financial assistance and educational programs, tens of thousands of patients and their families living throughout the United States and US territories receive essential assistance each year.

While case management services respond to the specific concerns of an individual patient or caregiver, our Health Services Research Initiatives shed light on the broad array of issues low-income patients confront during their healthcare experience. We examine how our patients get access to healthcare, how much care costs impact their treatment choices and goals and what happens to our patients as a result of their barriers to care. Experiences reported from people served through PAF's efforts and collective input from patients and caregivers about what they need and value fuels NPAF's person-centered public policy agenda.

Response to ICER's Proposed Changes

Value Assessments Grounded in Patient Perspectives and Priorities Should Be the Gold Standard

Value-based care's critical objective is to improve patient lives based on the priorities they articulate –not presumptions about value from the perspective of payers, providers, or industry. PAF research indicates that patients and caregivers are very aware of and concerned about rising health care costs and the impact on them. Indeed, they bear the brunt of this burden and want access to interventions that are reliably effective, available and affordable to address their illness and preserve function and quality of life without breaking the bank and causing extreme financial distress for themselves or their families. Patient surveys conducted among the vulnerable populations PAF serves consistently reveal that they are far more concerned about cost and its accompanying distress than potential side effects or the possibility of dying.

Patients typically receive healthcare services from a multitude of providers and facilities and there are costs associated with each. Medical debt mounts quickly, at the very time when their ability to pay is hardest. Patients' inability to access and afford necessary healthcare and maintain their financial stability creates emotional trauma that impacts their overall health. Moreover, when people become ill, or live with a chronic disease, their income is almost always impacted. As a result, many patients cannot sustain their basic needs such as housing, transportation, food and utilities. This broader constellation of total costs is neither acknowledged nor considered in ICER's current approach to expenditure calculations.

We understand that ICER's value framework applies a population-based approach. Nevertheless, integrating patient perspectives and priorities meaningfully and consistently as part of evaluating the quality and value of particular interventions is also paramount to ensure the assessments actually reflect what is important and relevant to them. NPAF is encouraged by ICER's stated intention to amplify use of real-world evidence (RWE) in its methodology, as well as the possibility of partnering with others to generate new RWE. Capturing data reflecting patient and caregiver lived experiences and person-centered care preferences and health outcomes are essential aspects of calculating and reporting value accurately. NPAF stands ready to serve as a resource in supporting ICER's efforts to integrate and generate more patient-reported and other person-centered RWE to serve as data sources guiding future value reviews.

QALY is Not the Gold Standard for Promoting Person-Centered, Value-Based Care

ICER's depiction of QALY as the "gold standard" belies the many concerns that have been documented regarding its validity as a reliable and equitable person-centered approach to value assessment. Multiple entities in the patient advocacy community have supplied consistent, detailed and accurate arguments against ICER's renewed reliance on QALY and evLYG analyses, including the National Health Council, Partnership to Improve Patient Care, and the Headache and Migraine Policy Forum, among others. NPAF shares these same concerns and urges ICER to reconsider its rationale and recognize QALY's potential harms and limitations in achieving the objective of ensuring equitable access to quality treatments that are valuable for all populations in need.

Including Patient and Caregiver Expertise Drives Better Value Appraisal Outcomes

Patient engagement requires eliciting and honoring their expertise and insights as equal partners throughout the appraisal process. NPAF appreciates that ICER is taking additional steps toward more meaningful engagement, such as including a patient perspectives report chapter and providing stakeholder briefings on assessment processes and findings. But these strategies still do not embed patient perspectives into the actual value analysis process continuously from beginning to end, and therefore miss the opportunity for ICER to be fully informed and responsive to people's unmet needs. For example, ICER's emphasis on return to work/productivity fails to account for the priority and value that patients and families also place on functional restoration to improve their quality of life and reduce caregiver burden and costs.

In addition to including informed and experienced patient and caregiver and clinical professional perspectives as part of the appraisal committees, ICER should also solicit input from these stakeholders about the types of seminar/webinar outreach topics and other patient engagement initiatives that would be most helpful. Indeed, it is equally important for ICER to consider the value of embedding patients as faculty to share their perspectives in this outreach to demonstrate a real commitment to the enhanced engagement efforts ICER describes. A timely co-created seminar on the strengths and limitations for RWE generation that includes patient-reported and caregiver-reported outcomes and action steps for collaboration to garner more relevant patient data is just one example of topics that should be considered. Further research on caregiver effects to quantify these costs and address existing areas of uncertainty would also be a worthy and relevant topic to pursue in developing new areas for RWE generation.

Conclusion

NPAF believes that patients and caregivers are ready and able to provide their perspectives on what value particular treatments or services bring to their lives. Equipping patients and caregivers with the resources, skills and services information they need to identify, communicate and advocate about their personal values and needs is at the core of NPAF's mission to put people at the heart of healthcare. We urge ICER to continue increasing its receptivity to patient and caregiver perspectives and expertise in shaping its work, and we look forward to ICER's release of a thoughtful and responsive revised framework in mid-December. Please contact me at Rebecca.Kirch@npaf.org or 202 277-5912 if you or ICER colleagues would like to further discuss our recommendations.

Sincerely yours,



Rebecca A. Kirch
Executive Vice President, Health Care Quality and Value



October 18, 2019

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RE: Proposed Changes for 2020 Value Assessment Framework

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson:

The National Pharmaceutical Council (NPC) appreciates ICER's call for public comment on the proposed updates to the 2020 Value Assessment Framework methods and procedures.¹ NPC especially appreciates the addition of language to ICER's conceptual structure that emphasizes "Fair Access" and "Future Innovation." In the past, the media reporting and payer use of ICER's reviews has focused almost exclusively on the "Fair Price" piece of ICER's conceptual structure, not recognizing that the structure is a three-legged stool: without payer commitment to fair access, future innovation will suffer. When innovation suffers, so do patients, health outcomes and society.

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)*,² and in our June 10, 2019 comments on changes needed to ICER's 2020 Value Assessment Framework,³ 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.

Although ICER's proposed updates provide several incremental improvements toward aligning with the *Guiding Practices*, further revision and refinement of the framework is necessary to truly support optimal value for patients. 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's June 10, 2019 comments called for 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 co-base case
- Increase subgroup analyses
- Include real-world evidence
- Quantitatively integrate additional benefits/contextual considerations
- Lay the groundwork to replace or augment cost-per-quality-adjusted life year (QALY)-based methodology
- Leave budget impact assessment to the end user
- Eliminate assessment of affordability and use of artificial affordability threshold

ICER acknowledged six of these areas in the proposed updates to the 2020 framework and made changes in four of them. NPC believes more substantial changes are needed in all eight areas and has added a ninth area: "Do not cross-reference with German Evidence Ratings."

A. Recommendation: Include Societal Perspective as a Co-Base Case

ICER acknowledged this recommendation and declined to include the societal perspective as a co-base case. ICER wrote, "Decision-makers in the U.S. health care system are not responsible for making trade-off decisions that involve broader societal resources." *NPC strongly disagrees with this statement; states, employers and other payers do indeed face such trade-offs and broader societal decisions.*

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).⁴ NPC's 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.

ICER has stated it will include a societal perspective as a co-base case when the "societal costs of care for any disease are large relative to the direct health care costs." ICER should clarify the criteria for this as there is overlap between treatments for ultra-rare conditions, "Single or Short-term Transformative Therapies (SSTs)" and traditional therapies.

NPC recommends that ICER include the societal perspective as a co-base case in all reviews and include the results from the societal perspective co-base case in all result summaries, such as press releases and report-at-a-glance documents.

B. Recommendation: Use a Collaborative Model to Achieve a Realistic Base Case

ICER did not acknowledge this recommendation explicitly, but is proposing to add a new section on “Controversies and Uncertainties” to “expand discussion of any alternative model structures or inputs suggested by manufacturers or other stakeholders that differ importantly from the base case.” NPC supports the addition of this section but urges ICER to go further than merely expanding discussion of alternative models. Qualitative discussion of alternative models is not enough; a quantitative exposition of the way cost-effectiveness results change under these models is needed, too.

The *Guiding Practices* underscore the importance of ensuring that the foundation for all assessment results, the base case, is realistic (Guiding Practice X). 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).⁵ 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 and the resultant range of model results.

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, modeling approach and results. These differences should be included in press releases and report-at-a-glance documents.

C. Recommendation: Increase Subgroup Analyses

ICER acknowledged this recommendation but declined to make any changes to subgroup analysis. NPC believes the need for appropriate subgroup analyses continues to be important.

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 (VBPs) for the various analyses. At a minimum, ICER should describe the heterogeneity of the population and estimate what proportion of the disease population are represented in their analyses to allow transparency in understanding where results would and would not apply. 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. VBPs should be estimated for these analyses, and the full range of VBPs should be included in result summaries such as press releases and report-at-a-glance documents.

D. Recommendation: Include Real-World Evidence (RWE)

NPC is pleased that ICER has acknowledged this recommendation and reaffirmed its commitment to using RWE. NPC will be watching to see the extent to which this commitment translates into action,

particularly when it comes to instances where RWE is discarded in favor of the exclusive use of randomized clinical trials (RCTs).

Guiding Practice XXII emphasizes that assessments should use the best available evidence. ICER's assessments rely heavily on evidence from traditional 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 supplement RCT data to inform payer decision-making and answer for whom the treatment works.

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. 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.

ICER also stated in its proposed updates it will "seek opportunities to generate new RWE for incorporation in reviews." NPC does not believe that ICER should undertake the generation of RWE. ICER does not have the resources to expand into this arena. While ICER should encourage others to conduct high-quality RWE that fills gaps in the knowledge base, we do not believe this is an appropriate role for ICER.

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. NPC recommends against ICER generation of RWE.

E. Recommendation: Quantitatively Integrate Additional Benefits/Contextual Considerations

ICER acknowledged this recommendation but declined to quantitatively incorporate additional dimensions of value. 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 quantitatively 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. This approach is insufficient and does not quantitatively 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.

ICER noted it attempted to pilot MCDA in 2009-2010 and found it difficult to use. NPC urges ICER to pilot MCDA in its 2020 assessment process. MCDA methods have evolved over the past decade, and the time period in which ICER piloted MCDA pre-dates ICER's value assessment framework by many years.

NPC recommends that ICER partner with researchers at organizations such as the Center for Enhanced Value Assessment (CEVA), Pharmaceutical Value (pValue), and the Innovation and Value Initiative (IVI) to pilot a consistent and transparent methodology to quantitatively incorporate these important factors in ICER's value assessments.

F. Recommendation: 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, ethical considerations, methodologic issues and disease-specific considerations.⁶ ICER itself has identified key problems with the QALY.⁷ 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 payer, population and disease.⁸ Evidence exists that willingness to pay for life-saving conditions is more than that for minor conditions,⁹ 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.¹⁰ Willingness to pay for oncology suggests thresholds that are much higher than what ICER currently uses as an upper bound.^{11,12} Some real-world coverage decisions in the U.S. are similarly consistent with higher willingness to pay (WTP) thresholds.

These signals of potentially higher or variable 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 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.

ICER acknowledged this recommendation and raised the upper bound in the core framework to \$200,000 per QALY. However, ICER lowered the upper bound for ultra-rare disorders from \$500,000 per QALY to \$200,000 per QALY. While NPC supports an increase of the upper bound in the core framework, it is disappointing that the upper bound will not be used for value-based price benchmarks and will not be presented in report-at-a-glance summaries. It is even more disappointing that the upper bound for ultra-rare disorders has been dramatically lowered, given the evidence presented above that there is higher WTP for such conditions.

NPC recommends that this uncertainty about U.S. WTP for various diseases and scenarios be addressed in the short run by using a wide range of cost-per-QALY thresholds in analyses and including the results from the full range in press releases and report-at-a-glance documents. In the long run, this should be done by developing and testing alternative value assessment methodologies to replace or augment the cost-per-QALY based methodology. NPC further recommends that the upper bound threshold for ultra-rare diseases remain (at least) at \$500,000 per QALY.

G. Recommendation: Leave Budget Impact Assessment to the End User

ICER acknowledged this recommendation but declined to drop the estimation of national budget impact from its assessments. 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. ICER’s estimates of national budget impact, however, are not relevant to these payers or useful for their decision-making purposes. Payers should estimate budget impact for their own populations, which are smaller and different than the overall U.S. population.

ICER proposed the addition of per-patient budget impact estimates, which are more useful to a payer seeking to use an ICER report than a hypothetical estimate of national budget impact. However, the addition of this per-patient budget impact highlights the false sense of precision that is inherent in ICER reviews, as mentioned above in section I.C. Cost per patient will vary by payer, both broadly (e.g., Medicaid, Medicare, employers) and narrowly (e.g., different commercial plans). While NPC believes a per-patient budget impact estimate is preferable to a national budget impact, if included, this estimate should include ranges so the individual payer can customize their own estimation of budget impact.

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. If included, per-patient budget estimates should include ranges to accommodate the variability across payers who will use these estimates.

H. Recommendation: Eliminate Assessment of Affordability and Use of Artificial Affordability Threshold

ICER did not acknowledge this recommendation in its proposed updates. NPC strongly believes the estimation of affordability and use of an artificial affordability threshold is inappropriate and has unintended consequences.

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 national 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.

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 and NPC demonstrates that ICER's affordability threshold could lead to an inefficient allocation of health care resources.¹³ 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.

NPC recommends that ICER eliminate its assessment of affordability and its use of an artificial affordability threshold.

I. Recommendation: Do Not Cross-Reference with German Evidence Ratings

A new issue that has emerged with the 2020 proposed updates is ICER's proposition to introduce evidence ratings designed to crosswalk to the German categories of “added benefit.” Guiding Practice XXVII cautions against misuse of value assessments by an unintended audience. ICER notes the many important distinctions between the methods used by ICER and the German system, which all serve to underscore why such a cross-reference could be misleading and is ill-advised. Drug comparisons in Germany occur in an environment that is not analogous to the U.S. due to differences in factors such as population, treatment options and comparators, endpoints, treatment guidelines, and health care resource utilization.

ICER's creation of a “rough algorithm” that relies on different methodologies and assumptions from the German system yet provides output in the same format, is described as a way to “spur further dialogue and calibration of evidence assessments across important pharmaceutical markets.”

However, translating ICER's assessments into the German categories in an approximated manner, laden with implicit assumptions, creates the opportunity for far more than dialogue: it creates the opportunity for misuse by creating the false impression that this output could be used in the German market.

NPC strongly recommends that ICER reconsider this proposal and drop the cross-reference with German Evidence Ratings from its 2020 Value Assessment Framework update.

II. Improvements to the Assessment Process

NPC's June 10, 2019 comments called for 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 models and inputs publicly available
- Extend length of time for review
- Establish a disease-specific working group of clinicians for each assessment

ICER acknowledged and made changes to two of these areas in the proposed updates to the 2020 framework. NPC believes more substantial changes are needed in all four areas.

A. Recommendation: Include Broader Results in Press Releases and Report-at-a-Glance Documents

ICER did not acknowledge this recommendation in its proposed updates. NPC believes it is critical that the uncertainty and full range of results are highlighted in summary documents so that end users will not have a false sense of the precision of ICER's estimates and hence misuse them.

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 when reported in summary documents, 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 the VBP 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 also 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 and considered in their decision making.

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 VBPs, as well as the confidence intervals around these prices.

B. Recommendation: Enable Full Transparency and Reproducibility by Making the ICER Models and Inputs 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 2018.¹⁴ 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.¹⁵ 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.

ICER acknowledged this recommendation but is making minimal change beyond expanding the pilot program to now include all ICER reviews. While it is a positive that manufacturers will have broader model access for all reviews, the limitations noted in the above paragraph remain. All stakeholders should have unrestricted access to the models.

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. Recommendation: Extend Length of Time for Review

ICER acknowledged this recommendation and is extending the review time for large class reviews by nine weeks. NPC appreciates this extension but notes that review time continues to be inconsistent with timelines used by the government and other health technology assessment (HTA) bodies. Guiding Practice IV notes that public comment periods need to be long enough to allow for comprehensive review of materials and submission of comments.

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, consistent with that allowed by other HTA bodies and the government.

D. Recommendation: Establish a Disease-Specific Working Group of Clinicians for Each Assessment

ICER did not acknowledge this recommendation. NPC urges ICER to reconsider the need for 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 section 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

ICER did not acknowledge this recommendation. NPC believes this is an oversight that does the U.S. health system a grave disservice. 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’s goal of “a more effective, efficient, and just health care system.”¹⁶

Drug spending accounts for only 16% of the U.S. health care dollar.¹⁷ 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 be magnified if its agenda was less concentrated and considered other interventions proportionately.

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 proposed 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,

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Chief Science Officer

Kimberly Westrich, MA
Vice President, Health Services Research

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Our Mission: To drive efforts to cure psoriatic disease and improve the lives of those affected.

October 18, 2019

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
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Boston, MA 02109

RE: **ICER Proposed Updates to 2020 Value Assessment Framework Methods and Procedures**

Dear Dr. Pearson,

On behalf of the National Psoriasis Foundation, and the more than 8 million individuals living with psoriatic disease, I write to you today to offer comments on the Institute for Clinical and Economic Review (ICER) *2020 Value Assessment Framework Methods and Procedures Proposed Updates* released on August 21, 2019. The National Psoriasis Foundation has had the unique experience of participating in both a value assessment on systemic psoriasis therapies in 2016, and a condition update in 2018. Throughout both reviews, our goal was to ensure that the perspective of individuals living with psoriatic disease were properly considered and reflected in discussions regarding the value of therapies. We thank ICER for accepting our feedback on these experiences, and have noted a number of improvements since 2016. We offer the following comments now as part of our continued commitment to elevating the experience of individuals living with chronic diseases in value assessments. We appreciate ICER's consideration of these comments as you refine and finalize the 2020 value assessment framework.

The Use of Real World Evidence

The National Psoriasis Foundation is pleased that ICER has listened to patient advocacy organizations and is reaffirming its commitment to using existing real-world evidence (RWE) and exploring new collaborative relationships with organizations to generate RWE that can complement published data sources. As the National Psoriasis Foundation has noted in the 2018 condition update, there are often disconnects between individual patient frustrations and the focus of various outcome measures. As ICER noted during the prior psoriasis reviews, the March 2016 FDA Patient Focused Drug Development (PFDD) meeting provided great insight into the significant quality of life impacts of this disease and the challenges in trying to manage each of the symptoms – including itch and pain – that often accompany moderate to severe disease. We were pleased that the model inputs in the condition update continued to extend beyond disease-specific measures such as the PASI, to include symptom improvement, treatment-related adverse events, health-related quality of life, and systemic manifestations, as well as data for evidence about the comparative effectiveness of targeted immunomodulatory in affecting domains such as itch, scaling, pain, quality of life, work productivity, and satisfaction with treatment. We noted the addition of 'satisfaction with treatment' was new to this 2018 condition update among the domains considered. This sort of expansion of evidence is critical to ensuring that the data reviewed by ICER during value assessments accurately reflects the challenges of living with chronic disease. We encourage ICER to continue to move in this direction and remain open to supplementing published data sources with additional real world evidence.

The Use of Multiple Cost-effectiveness Outcome Measures

The NPF has reiterated consistently in teleconferences, comment letters, and public dialogues the serious nature of psoriasis and the associated significant morbidity and increased mortality.^{i,ii} Significant attention has also been dedicated in NPF comments to the widespread prevalence of disease, and way in which it “significantly decreases health-related quality of life.” As we have noted in previous comment letters, while the NPF appreciates that ICER has given greater attention to these issues (including in the 2018 condition update), on behalf of the patient community we continue to stress the challenge of measuring a chronic disease such as psoriasis with the measures (QALY, PASI, BSA, etc) and tools available today. The NPF appreciates that ICER is striving to ensure that the information considered does not discriminate against any patient group.

Creating a New Process for Re-evaluating Evidence

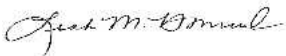
As ICER considers the process for reassessing whether new evidence has emerged that should be included in an update to the report, the NPF would urge ICER to be cognizant of the many resources that stakeholders must expend to participate in any condition update. As we noted in our 2018 review, participating in a condition update soon after an initial value assessment is a major undertaking for a patient advocacy organization. Ensuring that an update is not burdensome on the patient community must be considered as part of the decision to update.

Conclusion

Throughout the 2016 and 2018 ICER reviews, the NPF has acknowledged the benefit of bringing forward sound science and evidence that informs patients and providers about treatment options. We thank ICER for including the perspective of individuals living with psoriatic disease in both reviews, and considering the input of the patient community in updates to the value assessment framework.

As we have previously stated, we believe we have a shared goal – to reduce the 55% of patients with moderate to severe psoriasis who are not being treated to the appropriate standards of care. And to achieve that goal, we are going to need to engage every stakeholder who has an interest in the psoriatic disease community from value modelers, to payers, to pharmacy benefit managers, to physicians, to patients themselves in this dialogue. On behalf of National Psoriasis Foundation, thank you for your consideration of these comments.

Sincerely,



Leah M. Howard, J.D.
Chief Operating Officer

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PARTNERSHIP TO FIGHT CHRONIC DISEASE

October 18, 2019

Dr. Steven D. Pearson
President
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Boston, MA 02109

RE: Public Input for 2020 Value Assessment Framework

Dear Dr. Pearson:

The Partnership to Fight Chronic Disease (PFCD) respectfully offers comments on ICER's 2020 Value Assessment Framework: Proposed Changes, as issued on August 21, 2019, with a focus on issues of concern to persons with chronic conditions, including rare diseases and multiple conditions. PFCD understands that the revised version shared in August covers areas of proposed change as well as areas where no changes were made.

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 provide comments.

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 sustainability. That requires a focus on patient-centered and informed strategies for understanding health care value

¹ National Health Expenditures Accounts, CMS, December 2018

and effectiveness holistically, and in support of health care investments and outcomes that have meaning to all Americans.

PCFD appreciates the opportunity to contribute to the evolution and improvement of ICER's 2020 Value Assessment Framework and related practices and models, prior to release of the final version later this year. PCFD insights and recommendations follow:

General Thoughts and Recommendations

ICER and others utilize 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. The limitations of the perspective provided necessarily limit the contribution assessments of value provide to decision makers and, perhaps even more importantly, to the advancement of the value-driven care evolution as a whole. Well-designed assessment models that recognize the importance of personalized care, account for both effect on medical costs, individual and population health outcomes, caregiver burden, disability, and overall economic benefits. As such, they have potential to improve the management of chronic diseases, slow their spread, and prevent people from developing multiple chronic conditions.

Value is a function of both quality and cost, but significant limitations on quality measures particularly for people with multiple and/or complex chronic conditions hinder the definition and measurement of quality outcomes. 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. Value assessments should acknowledge this weakness and condition judgments made based on it.

We urge ICER to integrate dimensions of value described as “other potential benefits” and “contextual considerations” in equal standing with or better yet, instead of QALYs.

Comparative Clinical Effectiveness

PCFD is encouraged that ICER reaffirms its ongoing commitment to seek and use real-world evidence (RWE) in its reviews. RWE will enhance ICER's 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 study and use of these data in value assessments are often limited by a lack of transparency in research methods.² While multiple factors influence access and use of such data, ICER has an opportunity to promote transparency and appropriate utility to capture the benefit of RWE. We fully support ICER's incorporation of real-world evidence in its 2020 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.³ 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 forward, incorporation of real patient preferences as individuals not averages into the process of assessing the value of a set of health care options and investments merits attention.

ICER should 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. We call on ICER to expand patient engagement in research and deliberations, improve transparency, and patient-oriented communications and education. Such efforts will strengthen value assessment and utilization with patients as partners.

ICER's insertion of a crosswalk between its evidence ratings and the German health technology assessment (HTA) system is unproductive. Health care systems in the United States and Germany are inherently different, shaped by unique cultural norms, tax and financing systems, delivery system, and expectations. We recommend that ICER drop this plan and focus on improving its current assessment methods and process to better reflect aspects of values held by all Americans and speak to the strengths and needs of the U.S. health care sector.

Long-Term Cost Effectiveness

Looking Beyond the QALY

² Six Ways to Make Real-World Evidence Methods More Transparent; E.V.I.dently Today Blog; 6/20/19

³ Muhlbacher A. *Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions: The European Union Perspective*. Value in Health. 2016

PFCD finds ICER's resistance to abandon or at least substantially supplement Quality-Adjusted Life Years (QALY) and Equal Value of Life Years (evLYG) methodologies troubling. On behalf of people with chronic conditions and disabilities, PFCD reiterates strong objection to ICER's view that the QALY is the "gold standard for measuring how well a medical treatment improves and lengthens patients' lives".⁴ In reality, QALYs and evLYGs are increasingly seen as controversial, flawed and discriminatory methods for assessing value, and should be dropped or greatly diminished in use in favor of new methodologies that better reflect a broader view of value without adoption of discriminatory assumptions as to the value of individuals with disabilities. Innovation in health care has grown exponentially since the QALYs introduction; it's more than time for measures of value to innovate to keep pace.

Current assessment models too often reflect population and large group experience, are generalized, and, as a result, are biased relative to individual patients, their health status, and real-life circumstances. For people living with multiple or otherwise complex chronic conditions, QALY and 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.

We urge ICER to abandon or at least substantially supplement QALY and evLYG metrics in its work and adopt metrics that reflect patients holistically and their interactions across the spectrum of health care. ICER should consider evaluating care delivery models, use of medical technology, and other aspects of health care treatment and prevention to model.

Evaluating SSTs

On September 6th, PFCD shared recommendations for ICER on "single or short-term transformative therapies (SSTs) with a focus on issues of concern to people living with chronic conditions. Novel treatments require novel approaches to assessing value that must include open consideration of a variety of perspectives and expertise, including those with divergent viewpoints.

We agree with ICER's characterization of the challenges presented in assessing the value of SSTs, including uncertainties at launch, accrual of benefits over long periods of time, high upfront costs, and added dimensions of value. Given the stakes involved, challenges presented, and need for novel approaches, we were disappointed to see that in developing this proposal, ICER limited its consultation with U.S. health economists to those with which it already has existing relationships on ICER's existing models.⁵ Development of the proposed methods, key assumptions, and policies of what to include and exclude should involve a variety of perspectives, not merely seeking verification of proposed methods from experts already vested in the existing model.

Open comment periods are appreciated and helpful, but are much less effective in shaping assumptions, models and methods than in the genesis of such proposals when consulting with

⁴ Institute for Clinical and Economic Review, 2019; 2020 Value Assessment Framework - Proposed Changes, pg. 11

⁵ ICER Technical Brief, Table A3. University of Washington: <https://blogs.uw.edu/uwicer/project-team/>; University of Colorado-Denver: https://pharmacy.ucsd.edu/sites/pharmacy.ucsd.edu/files/Campbell_presentation.pdf.

and being open to expertise and diverging opinions has greater impact. To that end, we recommend that ICER revisit its proposal and, after consulting with a wide variety of experts, present a new approach to evaluating SSTs that captures the significance SSTs represent and the need for novel approaches for assessing value.

Including Controversies and Uncertainties

ICER proposed a new sub-section on “Controversies and Uncertainties” to boost transparency and allow exploration of different model variations that could be viewed as more conservative or optimistic.⁶ This sub-section will expand discussion of any alternative model structures or inputs suggested by manufacturers or other stakeholders that differ importantly from the base case. We fully support the addition of this new subsection as a dedicated space to generate greater transparency, something that PCFD wants to see reflected across all areas of ICER activity, and feature the array of value assessment models available to inform and improve the ICER value framework, promoting “transparency to patients, disclosing assumptions and inputs to patients in an understandable way and in a timely manner.”⁷

Other Changes & Priorities

Presenting a Societal Perspective

We strongly recommend 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.

Considering Subpopulations

PFCD supports ICER’s proposed changes that clarify that analysis of patient subgroups will be included in the framework. 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. For many people with autoimmune disease, for example, their experience of a disease is highly individualized and variable, including the manner in which their bodies respond to certain medicines. And 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, subgroup and scenario analyses are needed to begin to capture their inherent heterogeneity and complexity, and be reflected in subsequent assessments and determinations.

⁶ Institute for Clinical and Economic Review, 2019; 2020 Value Assessment Framework - Proposed Changes, pg.22

⁷ National Health Council. Patient-Centered Value Model Rubric Released. March 28, 2016. Available online <http://www.nationalhealthcouncil.org/patient-centered-value-model-rubric-released>.

We support ongoing and meaningful improvements by ICER to actively build subgroup and scenario analysis into its assessment process to reflect the truly heterogeneous, often complex nature of this population.

Relying on Clinical Trial Data

ICER is relying on clinical trials for purposes unrelated to their design and intended use and drawing conclusions that are accordingly flawed without indication as such. Such trials are used to prove a concept and, by definition, need to limit variables that can affect outcomes.

We urge ICER to reduce its heavy reliance on clinical trials, as they typically exclude people with multiple chronic conditions.

Respecting and Incorporating Patient Perspectives

Persons living with one or more chronic diseases and their advocates are uniquely qualified to contribute personal, real-world perspectives concerning health and value. Yet, for people with chronic conditions and rare diseases ICER's practices leave them feeling disrespected, and their input clearly supplemental or ancillary or ignored. Reviews and report insufficiently demonstrate that patient views are actually heard, influence, and are incorporated into final value assessment determinations; and arbitrarily short windows for patient and other public comment, often just three-weeks in an otherwise much longer timeframe for report generation, limit patient and public comment.

ICER is urged 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 its work. Alignment with models for engaging patients in research at the Patient-Centered Outcome Research Institute (PCORI) 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. We recommend that patients, patient advocates, and specialists with expertise in the disease states and treatments under review be fully engaged in ICER's review/recommendation process, including incorporating patients as equal voting members in decision-making and reporting.

PCFD 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.

PFCD appreciates that ICER makes several proposed improvements to reporting timelines and content that are useful to patients and their advocates. Extension of the timeline for large groups is beneficial and the same period should be extended to reviews concerning small groups, rare and low-incidence diseases and related treatments. Extension of the time period by one week

proposed for the period for public comment is beneficial, but should be extended further, consistent with feedback from public stakeholders to ICER over a period of years.

PFCD finds ICER's statement that "Due to the rapid timelines for ICER assessments, the length of comments and comment period must be limited to ensure that ICER staff has adequate time to review and incorporate suggestions"⁸ to be insensitive. Given the stakes for patients and their advocates in ICER's work and ICER's expressed interest in incorporating patient perspectives, a longer, more accommodating climate for patient input is warranted. We recommend a twelve-month period for ICER review with at least six-months advance notice of review targets for all groups and treatments, with a longer period and longer comments allowed for public comment.

Lastly, ICER proposes to add a "Patient Perspective" chapter to its reports, with guidelines pertaining to this new section. While a positive step toward assuring that patient experience, expertise and recommendations are recorded for readers upon report publication, its inclusion as supplementary to ICER's analysis confirms precisely the perspective so many patients have expressed in commenting on ICER's reports: patient perspectives are included to "count" without actually factoring into ICER's assessment of value overall. Unless and until the patient perspective is included in ICER's actual *analysis* and not as an add-on, the perspective expressed in a recent op/ed penned by Patricia Goldsmith and Carole Florman of Cancer Care and echoed by patient advocates participating in the ICER review process will remain that "there is no 'there' there."⁹ We urge ICER to include the patient perspective meaningfully, and visibly in all aspects of its value assessment deliberation and review, recommendation and reporting.

* * *

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, including through this dialogue . Ongoing efforts to improve value assessment tools to help patients, physicians, payors, and other stakeholders to make informed decisions about all aspects of health treatments and care are critical.

Respectfully submitted,



Kenneth E. Thorpe, PhD
Chairman

⁸ Institute for Clinical and Economic Review, 2019; 2020 Value Assessment Framework - Proposed Changes, pg 40

⁹ Goldsmith P and Florman C, ICER's Concern for Patients: Where's the Beef? Stat. October 9, 2019, available online <https://www.statnews.com/2019/10/09/icer-concern-patients-wheres-the-beef/>.



Pfizer Inc
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October 18, 2019

Steven D. Pearson, MD, MSc - President
Institute for Clinical and Economic Review (ICER)
Two Liberty Square, Ninth Floor, Boston, MA 02109
Submitted via email: publiccomments@icer-review.org

RE: Proposed Changes for 2020 Value Assessment Framework

Dear Dr. Pearson,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the proposed changes for the 2020 Value Assessment Framework.¹ Pfizer's purpose is to deliver breakthroughs that change patients' lives. We focus our efforts in core areas where we believe Pfizer is best positioned to bring unique and much needed medicines and vaccines to enhance the health of patients, their families, caregivers, and society. With an ongoing discourse on measuring value and accompanying value-based frameworks, 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 update its 2020 Value Assessment Framework and its call for comments from a variety of stakeholders. Accurately assessing and establishing the value of medicines and vaccines is a complex undertaking, and thus deserves careful attention and continuous, collaborative efforts. While ICER is proposing some minor changes based on stakeholder inputs, Pfizer was expecting a more significant change to the current assessment process and the value framework itself to include the patient's perspective and increase process transparency.

We will address our comments and recommendations in the following focus areas:

- A. Comparative Clinical Effectiveness and Grading Approach**
- B. Beyond QALYs & Long-Term Cost Effectiveness**
- C. Potential Budget Impact Analysis (BIA)**
- D. Process Transparency and Inclusion of Relevant Stakeholders' Voice**

¹ ICER Proposes Updates to 2020 Value Assessment Framework Methods and Procedures. Institute for Clinical and Economic Review. https://icer-review.org/announcements/2020vaf_proposed_updates/. August 21, 2019.

A. Comparative Clinical Effectiveness & Grading Approach

1. Recommendation: Reinforce and increase use of real-world evidence (RWE) for reviews but we recommend ICER to follow ISPOR guidelines for RWE generation and submit the evidence to peer review journals

Pfizer commends ICER's reaffirmation of using existing RWE for consideration in evidence review. A value framework should leverage as much existing evidence as possible and not solely rely on randomized clinical trials (RCTs) given potential bias due to differences in end points and comparator selection.² While substantial RWE may not be available for newer products, this source of evidence can be reviewed for established medicines and therapeutic area class reviews. RWE and patient preference studies can provide relevant information for assessing the value of medicines beyond RCTs, especially for patient populations that were underrepresented or excluded in clinical trials. As innovative evidence pathways become more prevalent, it will be important to provide additional guidance on how ICER will fairly assess RWE for value assessments.

We also recommend utilizing RWE to address the limitations of QALYs. As previously suggested by Pfizer, willingness to pay, patient adherence, and persistence to therapy data from real-world settings could provide insight for appropriate thresholds for value-based pricing. There is also new interest in utilizing RWE to provide better data on variability in patient responses. ICER should consider the totality of evidence and clearly delineate how RWE will be assessed when available and how this will be graded and compared vs RCTs. It is also important that ICER clearly reports the inclusion and exclusion criteria used for deciding which RCTs and RWE to include in the evaluation.

ICER also stated that it will explore collaborations with organizations that may serve as sources of real-world data (RWD) in order to generate RWE. We welcome this effort and we hope that the aim is to generate RWE that address the QALYs limitations by leveraging collaborations with patient groups for analyzing patient data.

² Chandra A, Shafrin J, Dhawan R. *Utility of Cancer Value Frameworks for Patients, Payers, and Physicians*. JAMA. 2016;315(19):2069–2070. doi:10.1001/jama.2016.4915

However, we recommend ICER to follow the ISPOR guidelines whenever planning to generate a real-world data study.³ Transparency in the methodological approach used is going to be key to be able to carefully assess biases and rigor of the analysis. Additional guidelines can be gathered from the GRACE (Good ReseArch for Comparative Effectiveness) checklist, which is designed for the assessment of observational studies of comparative effectiveness for quality and decision-making.⁴ Moreover, RWE studies may require a long time. It would be great to understand if this will affect the timing of reports. RWE generation cannot be rushed, or the quality and generalizability can greatly suffer. A pre-specified protocol would be needed for any real-world study that external stakeholders should have a chance to review. This could have a major impact on timelines for reports and may need to be done in advance of a planned report rather than in parallel. We also encourage that if ICER decides to generate RWE, that it be submitted for publication to peer-reviewed journals.

2. Recommendation: Enhance transparency and replicability of grading approach

The proposed evidence rating matrix is subjective to biases and it is not aligned with the recognized GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach and the Evidence to Decision or Evidence to Recommendation (EtR) frameworks.⁵ The ICER framework has only two dimensions of assessing the evidence: 1) level of certainty and 2) comparative benefit.

We recommend ICER to compare their approach to the Advisory Committee on Immunization Practices (ACIP) approach for evidence grading and to utilize the internationally recognized GRADE approach instead of creating an ad hoc biased approach. The results of the ICER approach may differ from GRADE and may create more confusion than clarity.

3. Recommendation: Do not cross-reference with German evidence ratings

While ICER has provided a rationale of expressed interest in comparing ICER evidence ratings to other health technology assessment (HTA) groups' in other countries, Pfizer believes comparison

³ 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;26:1033–1039. <https://doi.org/10.1002/pds.4297>

⁴ 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 and Specialty Pharmacy*, October 2016; 22(10):1107-13.

⁵ Lee G, Carr W Updated Framework for Development of Evidence-Based Recommendations by the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2018;67:1271–1272. DOI: <http://dx.doi.org/10.15585/mmwr.mm6745a4>

with German ratings is deceptive due to differences in methods and the intention/purpose of such ratings across systems. Moreover, for evaluations performed at the time of launch in the US, the European label may not be available. Speculations on what the EU label may be versus the US is neither scientifically nor methodologically appropriate. Even as a complementary rating, specific to “added benefit,” this cross-referencing could lead to misuse by an unintended audience and assumptions could arise that certain outputs could be applied to German markets. Further distinction between the methodologies across the two ratings should be considered in removing this in the 2020 value framework. ICER has acknowledged within their own comments that the German assessment is based on very different methods. So why confuse readers who may not be familiar with the German system? In fact, it is the opposite of transparent to adopt the same rating scale with completely different underlying methods of assessments. This will confuse the readers and the issue as readers may either assume ICER uses the same methods as the Institute for Quality and Efficiency in Health Care (IQWiG) and misinterpret the strength and quality of ICER’s rating. Pfizer encourages that ICER is comparing their methods to other HTAs bodies as there is much room for improvement in how ICER performs their reviews, but it should not be included in the formal value assessment. Moreover, why did ICER select Germany? Even in the EU, each country has their own HTA body to address the specific needs of their respective systems based on their evidence-based grading process. While comparisons of the underlying methods of assessment for these bodies is interesting and may be a good topic for a manuscript, it does not belong to the evidence-based assessment in each specific country. It is unclear what is ICER objective in trying to translate the results of one assessment into the rating system of another and making label assumption (in the case the label is not even available). Furthermore, the purpose and intent of the additional benefits assessment in the German AMNOG system is specific and tailored to their overall healthcare system; we do not think it reasonable or informative to compare across systems with varying methods and intentions. In particular as the German health care system is very different from the US health care system.

B. Beyond QALYs & Long-Term Cost Effectiveness

4. Recommendation: Reconsider enhancement of QALY as a measure of health gain/dimension of value given its limitations or align thresholds per QALY accordingly (if QALY used)

Pfizer has previously recommended that ICER reconsider its use of QALYs in its Value Framework based on evidence recognized among health economists, policy makers, insurers, and patients.⁶ QALYs are limited in assessing additional dimensions of value as they do not capture the societal perspective as a reference case, patient heterogeneity nor include patient provided information (PPI). ICER continues to exclude recommendations from the Second Panel on Cost Effectiveness. The Panel emphasized that the societal perspective should include elements such as informal health care sector costs and relevant non-health care sector costs (Pfizer recognizes that costs such as social services, legal/criminal, justice, education, housing, and environment may be considered only for specific diseases and conditions).⁷ While ICER is not proposing any changes to the QALY and the equal value of life years gained (evLYG) analyses, Pfizer believes there is room for improvement to these measures including adding productivity, insurance value, and value of hope. A proposed alternative for an incremental cost effectiveness measure is the “Quality- and Risk-Adjusted Life-Year” (QRALY) developed by Lakdawalla and team, which does include the value of hope and insurance value.⁸ This should also be considered for curative and transformative treatments.

ICER states its continued use of the QALY as the “gold standard for measuring how well a medical treatment improves and lengthens patients’ lives...” that has been around for more than 30 years. Yet, new information and assessment of the QALY have been widely published—ICER acknowledges these limitations themselves.⁹ Pfizer acknowledges that ICER has tried to identify an alternative with evLYG. However, the evLYG also has limitations such as disregarding value for a treatment that does not prolong life (e.g. cure for blindness), therefore it is not a solution to QALYs limitations.

It is critical that ICER address the limitations of the QALY and evLYG in the 2020 Value Framework if they intend to provide fair and comprehensive input on value-based prices and justifiable price increases. Quantitative benefit-risk metrics that include patient preference weighting should be considered. If the QALY is used as is, then single cost-per-QALY thresholds should be excluded as they will not capture the full perspective of all health care stakeholders and vary by disease and population.

⁶ Neumann and Cohen (2018). “QALYs in 2018-Advantages and Concerns”. JAMA 319(24):2473-2474

⁷ Neumann et al. (2017) “Cost-effectiveness in Health and Medicine. Second Edition”. Oxford University Press.

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 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.

Willingness-to-pay (WTP) will also impact thresholds per QALY as they vary by condition, especially for rare and orphan diseases. While there has been no standard evaluation process for thresholds that include societal values. Overall, there is uncertainty with QALYs and current thresholds per QALY and we recommend ICER reconsider additional evidence and changes to these dimensions of value for the 2020 Framework.

5. Recommendation: Remove cost-effectiveness thresholds as standard for value-based price benchmark

Given the large uncertainty around CE thresholds (\$50k, \$100k, \$150k, \$200k) per QALY / evLYG overall and specifically in the diverse US health care system, we recommend ICER to report various threshold and avoid using a threshold range of \$100k – \$150k per QALY & evLYG as standard for value-based price benchmarks.

A single threshold does not capture the heterogeneity and complexity of the US health care system, perception of value by different stakeholders for different medications, and uncertainty in the analysis. Further, applying an ICER threshold value carries with it a number of detrimental assumptions (e.g. the health care budget is fixed, meaning that it cannot be exceeded, the one and only aim of health care decisions is to maximize health benefits, in terms of QALYs or in terms of LYG, within the population, [see Cleemput et al., 2008 for detail¹⁰]. It can also disincentive development of innovative medicines for populations with large unmet needs. Thresholds should vary by disease severity and by willingness to pay or opportunity costs of different stakeholders. If ICER decides to still use thresholds, Pfizer recommends that uncertainty about affordability thresholds for various diseases and scenarios be addressed in the short term through a workshop with health economists, payers, and patients, and in the long term by developing and testing alternative value assessment methodologies.

6. Recommendation: Include societal perspective as base case

As proposed in previous comments and as cited in the limitation of QALYs for not including societal perspectives, we recommend that ICER reconsider including societal perspective as the base case to more accurately reflect patient perspectives. Based on recommendations from the Second Panel

¹⁰ Cleemput I., Van Wilder P., Vrijens F., Huybrechts M., Ramaekers D. (2008). Guidelines for Pharmacoeconomic Evaluations in Belgium. Health Technology Assessment (HTA). Brussels: Health Care Knowledge Centre (KCE) KCE Reports 78C (D/2008/10.273/27).

on Cost-Effectiveness in Health and Medicine, including societal perspective as a base case can provide a broader perspective of costs including the impact of caregivers, labor productivity, and adherence. As more payers, including public ones, review ICER's research and opinions, it would be significant to include the societal impact on cost-effectiveness analysis (CEA) to reflect real-world behavior. This would augment CEA to be inclusive of different perspectives including that of patients and society overall.

7. Recommendation: Extend the number of sensitivity analyses performed to understand how robust the results are and their main drivers so that the discussion on Controversies and Uncertainties may be more meaningful

We welcome the inclusion of a “Controversies and Uncertainties” section to cost effectiveness to broaden discussion of alternative model structures and assumptions. However, the capability of fully discussing these controversies and uncertainties depends on the number and rigor used by ICER when performing sensitivity analyses. One sensitivity analysis and PSA should be performed for the major inputs. 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. Moreover, whenever ICER selects a model structure different from the main literature, they should provide information on the rationale for doing so as well as advantages and limitations.

C. Budget Impact Analysis (BIA)

8. Recommendation: Remove budget impact analysis from the value assessment

While ICER will continue to include a budget impact analysis (BIA) in its framework, Pfizer would like to reiterate the limitation of the BIA in agreement with the ISPOR BIA Guidelines II that “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.” We recommend ICER dismiss the estimation of the national budget impact from its assessments as this is not reflective as a measure of value. The BIM approach used by ICER is not aligned with the literature and guidelines on BIM. The affordability budget threshold used by ICER is not scientifically validated and not aligned with affordability challenges faced by payers. The end user should estimate budget impact on their own

accord and ICER should continue to focus on value. Payers should estimate budget impact for their own populations as these are different than the overall population. Additional clarity and rationale on why ICER would continue to include a BIA in their assessment when this is not helpful to formulary decisions is needed.

The addition of per-patient budget impact estimates will provide uncertainty as costs per patients will be different per payer and insurance plans. If this estimate is included, it should be accompanied with ranges to allow for payer discretion in estimating their own budget impact assessment. While ICER is providing greater details on its BIA procedures, Pfizer recommends that the BIA is removed as it is not reflective of value and pertains to formulary decisions, which payers should develop on their end.

D. Process Transparency and Inclusion of Relevant Stakeholders' Voice

9. Recommendation: Enhance the transparency, replicability, and validity of disease economic models by engaging with manufacturers, key clinical experts, and patients

To increase the reliability and reproducibility of ICER's models and evaluation of evidence, Pfizer suggests that ICER disclose their models to the public and include the totality of evidence in documents such as press releases and briefs. While ICER has attempted to share models via a pilot program, there is still room for improvement in the current framework – models and evidence reviewed should be unrestricted to all stakeholders for transparency and a better understanding of ICER's work. When presenting all available evidence in public documents, an example would be to include societal perspectives and clearly explaining the uncertainty surrounding a single value-based price by including a range of estimates.

Therefore, Pfizer recommends that the aim of sharing the disease model with manufactures 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. We acknowledge the effort to engage with clinicians during the model development phase that ICER has initiated. However, we would like to encourage ICER to do more to achieve the transparency and validity objectives. It is important that during the design phase of the disease model, ICER engages with more than one clinical expert and they should be in that specific disease area. 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. However, this should not be done in isolation. Often, we may have the desire to build a perfect model to then discover that we do not have data to input in the model and many assumptions need to be made which increases the uncertainty around results. Therefore, we recommend creating a round table including clinical experts in that disease area, health economists, patients, and manufacturers to design the most appropriate model structure given the nature of disease, patient perspectives, and clinical guidelines and data availability.

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. This should all be laid out in the scoping document and model protocol and any major changes to the approach need to be justified. This justification for the changes should be provided for public comment to increase transparency and avoid the situation that occurred with the recent RA review where the final model was dramatically different from original scoping document due to changes made seemingly independently by ICER and not based on public feedback.

Pfizer is continually committed to improving the health care system and improving patient's lives. We appreciate this opportunity to provide input to ICER's 2020 Value Framework. We hope that ICER reconsiders changes to their current proposals given the evidence provided. Value will continue to be contended by diverse perspectives and it will require robust clinical, scientific, and economic evidence partnered with patient provided information. Only then, can we have an inclusive and fair system in assessing the clinical and economic value of drugs and innovations.

Sincerely,



Cristina Masseria, MSc PhD

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October 18, 2019

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

Re: Call for Input on Proposed Revisions to 2020 Value Assessment 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) request for feedback on its proposed updates to the 2020 Value Assessment Framework methods and procedures. PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier and more productive lives. Since 2000, PhRMA member companies have invested more than \$900 billion in the search for new treatments and cures, including an estimated \$79.6 billion in 2018 alone.

PhRMA is also a long-standing supporter of using evidence as the basis for health care decision-making. Advancing better evidence and tools to support sound health care decision-making, including advancing the science of value assessment frameworks, is a core principle adopted by our members and is central to our policy agenda.^{i,ii}

Over the past several years, ICER has made several improvements to its value framework that align closely with PhRMA's principles for value assessment. However, ICER still has not incorporated many of the recommendations detailed in prior comment letters from PhRMA (and many other stakeholders). While we appreciate some of the steps ICER has taken, such as further incorporating real-world evidence (RWE) into the value assessment process and extending the timeline for review, many of the proposed revisions do little address the inherent flaws associated with the underlying framework. Further, the inherent flaws mean that ICER's assessments are more likely to cause avoidable access barriers if misused by payers or policymakers. As a result, we encourage ICER to develop a value framework that is relevant for a plurality of population-level decision-makers and trusted by the biopharmaceutical industry, patients and physicians.

To that end, we highlight our most fundamental concerns with ICER's framework in this letter. Our priority is promoting the development of sound evidence and value assessment tools, and ensuring they are used appropriately and in ways that do not impede patient access to medicines. Specifically, we recommend that ICER:

- I. Join others in the value assessment field in pushing beyond reliance on Quality-Adjusted Life Year (QALY) and Equal Value of Life Years Gained (evLYG)-based methods.

- II. Adequately and quantitatively account for a broader range of value elements and perspectives.
- III. Eliminate artificially low cost-effectiveness thresholds, particularly for treatments aimed at rare diseases.
- IV. Discontinue the incorporation of arbitrary and subjective budget thresholds into value assessments.
- V. Abandon the proposed comparison of evidence ratings between ICER and ex-U.S. countries which necessarily have different health systems, cultural values and preferences.
- VI. Commit to the full incorporation of externally-generated RWE in future reports.
- VII. Broaden the focus of assessments beyond drugs.

We appreciate ICER's consideration of our recommendations. PhRMA believes that, if these recommendations are adopted, ICER's value framework 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. Join others in the value assessment field in pushing beyond reliance on the evLYG and QALY-based methods.

At the forefront of PhRMA's concerns is ICER's continued reliance on flawed standards that fall short of patients' needs. ICER's decision not to explore methods beyond the underlying QALY- and evLYG-based framework represents a missed opportunity to join the movement towards a patient-centered, 21st century value-based health care system.

PhRMA has repeatedly outlined the shortcomings and controversies associated with the use of QALY-based cost effectiveness analyses (CEAs) in previous comment letters, and those concerns continue to be echoed among leading health economists, industry leaders, and patient advocates. The use of the QALY is highly problematic and does not align with the multifaceted and complex course of care patients often go through. As such, it is difficult to adequately translate and apply QALY-based assessments into real-world decision making in patient centered and clinically appropriate ways.ⁱⁱⁱ

One of several long-standing concerns among critics of QALY-based cost-effectiveness analyses is that cost-per-QALY ratios discriminate against select patient subgroups. This is particularly true in the case of seniors and persons with disabilities, who are less likely to experience potential QALY gains compared to younger and healthier individuals. It is also well established that the QALY cannot adequately capture the full spectrum of value elements and wide heterogeneity of patient preferences. By limiting focus to the average effectiveness of a treatment for an entire patient population, ICER is ignoring important clinical differences and patient preferences that help shape a therapy's value.

ICER's addition of the evLYG to its framework does not assuage our concerns about ICER's methods for determining long term cost effectiveness. In explaining the development of the evLYG, ICER states "...policymakers can be reassured that they are considering information that poses no risk of discrimination". While we appreciate ICER's acknowledgement that the QALY is discriminatory,

inclusion of the evLYG does not serve as an appropriate solution, as there are numerous limitations associated with the use of evLYG. Most notably, application of evLYG would not accurately convey value for conditions that do not reduce life expectancy, such as treatment for eczema or a cure for blindness. The evLYG would also value two medicines, one that reduces side effects and one that does not, as having equal value. We remain concerned that neither the QALY nor the evLYG properly capture the value of a medicine.

Since the ISPOR Special Task Force on U.S. Value Assessment Framework's recommendation for stakeholders to explore novel methods of value assessment, leading industry researchers and academics have proposed non-QALY methods that encourage stakeholder engagement and promote value-based decision making, such as multi-criteria decision analysis (MCDA). From 2017 to 2018, the number of published articles referencing MCDA increased nearly 30%. Over that same time period, stakeholders have continued to scrutinize QALY due to the metric's inability to capture the non-traditional value elements that matter most to patients, and its failure to capture the weight stakeholders assign to different value elements. MCDA offers a tremendous opportunity to address these and other shortcomings associated with traditional value assessment.

Applying MCDA would allow payers to assign weights to different elements of value and arrive at their own estimate of a treatment's worth. The flexibility of selecting relevant dimensions of value and specifying their relative importance encourages transparency and allows decision makers to have a comprehensive understanding of the health economic outcomes associated with treatments specific to characteristics of their own member populations.^{iv} While we recognize ICER has explored the use of MCDA in the past, researchers have since suggested MCDA methodologies are no longer conceptual in foundation and can be feasibly applied to coverage and reimbursement decision making.^v

If ICER continues to rely on QALY-based analyses to conduct value assessment, at a minimum it should consistently expand results to reflect all relevant patient subgroups based on different needs and preferences. ICER often fails to release value-based prices for all relevant subgroups, even when subgroup analyses are conducted as part of its assessment. It has been noted that decision makers often achieved considerable net benefit gains when accounting for heterogeneity in CEAs.^{vi}

To address the aforementioned issues PhRMA recommends the following:

- *Actively promote and incorporate alternative approaches to value assessment, such as multi-criteria decision analysis.*
- *Expand assessments and results to reflect all relevant patient subgroups based on clinical needs and preferences.*

II. Adequately and quantitatively account for a broader range of value elements and perspectives.

PhRMA remains concerned that ICER is not incorporating additional elements of value quantitatively in future assessments. With this decision, ICER continues to fall short of broad stakeholder consensus, including from its peers in the academic community, such as the ISPOR Special Task Force on U.S. Value Assessment. It is imperative that ICER's value framework remains aligned with both the best practices set forth by thought leaders in the field, and the needs of the stakeholder at the center of our

health care system – the patient. Incorporating these non-traditional value elements, the ones that matter most to patients, helps ensure decision makers are provided with comprehensive economic evaluations that can adequately assist in patient-centered coverage and reimbursement decision making.^{vii}

ICER has previously acknowledged that while non-traditional elements may play an important role in assessing value, the methodologies are too premature for adoption. However, we believe this view fails to acknowledge the significant progress being made in this area. Efforts by researchers to evaluate the quantitative incorporation of novel value elements has led to an influx of publications in the past year alone.

The PhRMA Foundation, for example, recently announced the winners of this year's Value Assessment Initiative Challenge Awards, which sought innovative and patient-centered approaches to measuring health care value.^{viii} One winning paper proposed a new method to incorporate risk and uncertainty into value assessments, including specifically measuring the value of reducing uncertainty (i.e. value of insurance) and the value of increasing the likelihood of positive outcomes (i.e. value of hope). Using simulations and a theoretical framework, the authors concluded that the incorporation of these novel value elements should not be overlooked and can have an impact on value estimates.^{ix} In a separate study, researchers summarized the empirical literature that pertains to augmenting cost-effectiveness analyses for four novel elements tied to uncertainty. A systematic review of the literature revealed that incorporating novel elements into cost-effectiveness analyses could impact the net monetary benefit of a medical technology or therapy by up to 30%.^x We remain adamant that ICER should work with these stakeholders to better understand how non-traditional elements of value can be feasibly applied to its own assessments. As it stands, ICER's failure to incorporate patient-informed value elements reveals an inherent bias to underestimate a therapy's true value and contradicts its public commitments to improve its framework.

In addition, we continue to urge ICER to include the societal perspective as a base case. When providing rationale against a societal base case, ICER stated, "Decision-makers in the U.S. health care system are not responsible for making trade-off decisions that involve broader societal resources." This is false – in fact, employers and other payers often do care about such trade-offs and the types of value elements relevant to the societal perspective, such as productivity and caregiver burden. PhRMA's support for use of a societal reference case is also echoed in the recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine, a reference point for many of ICER's methodological choices.^{xi}

To address the aforementioned issues PhRMA recommends the following:

- *Incorporate all relevant outcomes, including both traditional and non-traditional value elements, into its final value-based prices.*
- *Conduct long term cost effectiveness analyses using both a health system and societal perspective, and release value-based prices based on both perspectives.*

III. Eliminate the artificially low cost-effectiveness thresholds, particularly for treatments aimed at rare diseases.

PhRMA has several concerns with ICER's proposal to alter its cost-effectiveness threshold range. As PhRMA has stated in the past, and similarly to how a single QALY estimate cannot adequately capture

the many aspects of value or the wide heterogeneity of patient preferences, the use of a single, national-level threshold in ICER's reports proves of little value at the payer or societal-level. The diversity of health plans and member demographics across the payer landscape highlights the complex and multi-faceted nature of our health care system, and reaffirms the notion that a single, national-level threshold cannot be applied consistently across all end-users of ICER's reports. ICER's proposed revisions to its value framework do not sufficiently address these concerns.

We also disagree with ICER's proposal to apply a \$50,000 to \$200,000 range of cost per QALY thresholds to rare diseases. ICER's reversal of its prior decision to apply a \$500,000 cost per QALY threshold is contradictory to its own previous rationale for doing so and will threaten access to innovative therapies for patients with rare diseases if ICER's assessments are used by payers. It is concerning that ICER, which has previously acknowledged the significant and unique value that these therapies may hold for patients, has decided to revert to an artificially low cost-effectiveness threshold.

Furthermore, while we acknowledge that ICER is increasing the upper bound of its value framework to a \$200,000 cost per QALY threshold, ICER has not committed to applying it to estimate value-based price benchmarks or within report summaries. ICER's failure to translate cost effectiveness ratios for the upper bound threshold into value-based prices is not supported by any reasonable justification, leading PhRMA to conclude that ICER's goal is to artificially deflate the value-based price range.

To address the aforementioned issues PhRMA recommends the following:

- *Eliminate the arbitrary and subjective cost-effectiveness thresholds from all future reports; at a minimum, reinstate the \$500,000 cost per QALY threshold for treatments for rare diseases.*

IV. Discontinue the incorporation of arbitrary and subjective budget thresholds into value assessments.

In addition to the use of cost-effectiveness thresholds, PhRMA continues to have concerns with ICER's approach to measuring the budget impact of medicines. ICER proposes to make minor changes to the short-term affordability portion of its framework, such as inclusion of a per-patient budget impact, but those changes do not mitigate the numerous concerns stakeholders have raised over the technical and conceptual issues associated with ICER's approach.

As mentioned in our prior response letter, actuaries reviewing ICER's methods for assessing short term affordability suggested that not only were ICER's budget impact thresholds driven by variables unrelated to the value of a medicine, the arbitrary nature of the budget threshold calculation itself led to dramatic variation in results each year. They found that "GDP growth plus 1% is not consistent with either historical experience or expected future pharmacy cost growth" and would not result in calculating appropriate budget impact thresholds.^{xii} Research has found that applying ICER's methodologies during the 1992 to 2012 time period resulted in annual thresholds varying from \$1.36 billion in 2004 to *negative* \$607 million in 2009.^{xiii} Such volatility and inconsistency in results again raises the question as to whether budget impact thresholds should be incorporated in ICER's assessments.

Not only is ICER's methodology for calculating budget thresholds flawed, it could result in significant, inappropriate barriers to patient access, and subsequently, worse health outcomes. A recent study

assessed the hypothetical impact of applying ICER's budget impact threshold to Lipitor (atorvastatin) at launch. Had payers utilized the short-term budget impact threshold for formulary management, only 28% of the 2.9 million patients would have received the treatment in the five years following launch. Consequently, this restricted access to a life-saving therapy during the first five years on market could have resulted in approximately 72,000 additional major vascular events and nearly 19,000 additional deaths.^{xiv} The severity of ICER's incorporation of budget impact estimates in future reports should not be overlooked.

PhRMA reiterates its position that budget impact assessments should be left to the end user of ICER's reports, the payer, so they can apply the unique characteristics of their respective member populations. As mentioned previously, a single, national budget impact estimate used in future ICER reports would provide of little use for payers during coverage and reimbursement discussions as member population and demographics differ dramatically across regional and national health plans. Until ICER removes the arbitrary budget impact estimates from future reports, patient access to innovative and life-saving therapies will remain in jeopardy.

To address the aforementioned issues PhRMA recommends the following:

- *Eliminate the budget and affordability thresholds from value assessments.*

V. Abandon the proposed comparison of evidence ratings between ICER and ex-U.S. countries which necessarily have different health systems, cultural values and preferences.

In the proposed revisions to its value framework, ICER states its intent to compare its own evidence ratings to those from the Germany HTA organization IQWiG (Institute for Quality and Efficiency in Health Care). In justifying the proposal, ICER stated "...As ICER's work has gained use internationally, interest has been expressed in comparing ICER evidence ratings to those from HTA groups that provide similar reviews for policy making purposes in other countries."

We appreciate ICER's apparent interest in validating its ratings by comparing them to those used in other countries. However, we question the utility and appropriateness of comparing an assessment made in the U.S. context with one made in the German context. Comparing ICER assessments to Germany's risks pulling ICER closer to approaches employed in Canada and Europe in which national or regional government agencies use evidence ratings to delay and deny access to new medicines.

As prior research illustrates, assessments of comparative clinical and cost effectiveness can vary considerably from one country to another,^{xv} likely due to a variety of factors. These include the influence the overlying policy construct and, for comparative effectiveness reviews, the overlaying cost considerations. Additionally, countries' differing cultural value and preferences play a role. As mentioned previously, the U.S. healthcare system is highly decentralized, complex and market-driven. There are important differences between the German system and the ways in which we pay for and receive health care. For these reasons, we believe it would be inappropriate for ICER to crosswalk its comparative effectiveness findings with those of a German organization. Instead, we recommend that ICER make its models and assessments truly transparent, so they can be appropriately validated by researchers, patients, and caregivers in the U.S.

To address the aforementioned issues PhRMA reiterates the following:

- *Refrain from comparing ICER evidence ratings with ex-US countries.*

VI. Commit to the full incorporation of externally-generated RWE in future reports.

In its proposed update to its framework, ICER affirmed its commitment to utilizing any existing real-world evidence in its future assessments. While PhRMA believes that ICER's statement is a step in the right direction, we also urge ICER to commit to continue to expand its use of RWE beyond limited contexts and for certain purposes. We also hope ICER will provide a stronger, more explicit commitment to the formal incorporation of RWE into its quantitative assessments.

As demand increases for more RWE in cost-effectiveness analyses, it's imperative that ICER prioritizes the use of information most relevant to decision makers. Rather than giving preference to data from randomized controlled trials, PhRMA remains adamant that ICER should give appropriate weight to real-world evidence that adequately reflect the member population and characteristics of end-users. Additionally, while PhRMA is supportive of ICER's use of RWE, we are very concerned with ICER generating RWE for the sole purpose of using it in an ongoing value assessment, in absence of peer review. In order to avoid raising questions regarding the objectivity and validity of the RWE being relied on, ICER should avoid generating its own RWE, and focus its efforts on fully and appropriately incorporating externally-generated it into assessments.

To address the aforementioned issues PhRMA recommends the following:

- *Fully incorporate all existing and future real-world evidence data in Final Reports to ensure end-users have data relative to their respective member populations.*

VII. Broaden the focus of assessments beyond drugs.

Prescription medicine spending is a small and stable share of health care spending. Retail and non-retail prescription medicines account for just 14% of total U.S. health care spending.^{xvi} Despite continued emphasis on improving value and reducing spending across the *entire* system, ICER's assessments, along with most cost effectiveness analyses, have historically been disproportionately focused on drugs. The field's disproportionate focus on pharmaceuticals was reinforced in a recent study published by the Research Consortium for Health Care Value Assessment in which researchers found that nearly 46% of all cost-effectiveness analyses evaluated pharmaceuticals.^{xvii} PhRMA urges ICER to set itself apart by expanding its focus on other sectors of healthcare spending, including hospital care and physician and clinical services, which account for 31% and 18% of overall healthcare spending, respectively.^{xviii}

Furthermore, PhRMA encourages ICER to improve the overarching health care system by expanding the scope of its mission to include reducing the use of low value care. It is estimated that each year, approximately \$158 to \$226 billion dollars is spent on wasteful or low-value care services, including health care services that provide little or no clinical value to patients.^{xix} If ICER were to place equal focus on eliminating low value care as it does on the assessment of pharmaceuticals, it could lead to meaningful change within the health care system, including the reduction of significant waste and the generation of savings. It would also more closely align ICER with its mission to facilitate the shift towards a value-based health care system.

To address the aforementioned issues PhRMA recommends the following:

- *Expand ICER assessments beyond pharmaceuticals to include non-drug services and services deemed “low value”.*

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.



Randy Burkholder
Vice President, Policy & Research



Lauren A. Neves
Senior Director, Policy & Research

ⁱ PhRMA. “Policy Solutions: Delivering Innovative Treatments to Patients.” Available at: <http://phrma-docs.phrma.org/sites/default/files/policy-solutions.pdf>

ⁱⁱ PhRMA Value Collaborative. More information available at: <http://www.phrma.org/advocacy/the-value-collaborative>

ⁱⁱⁱ 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/>

^{iv} 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>

^v Phelps, C. Expanding Use of Multi-Criteria Decision Analysis for Health Technology Assessments. 2019. Available at: <http://www.phrmafoundation.org/wp-content/uploads/2019/09/Expanding-Use-of-Multi-Criteria-Decision-Analysis.pdf>

^{vi} Kohli-Lynch, C., Briggs, A. Heterogeneity in Cost-Effectiveness Analysis. Economics and Finance. 2019. Available at: <https://oxfordre.com/economics/view/10.1093/acrefore/9780190625979.001.0001/acrefore-9780190625979-e-101>

^{vii} 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)

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- xvi Roehrig C; Altarum Institute. Projections of the prescription drug share of national health expenditures including non-retail. <https://altarum.org/publications/projections-prescription-drug-share-national-health-expenditures-including-non-retail-0>. Published June 2019. Accessed June 2019.
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- xviii Centers for Medicare & Medicaid Services. National Health Expenditure Data. Updated 2018. Available at: <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/highlights.pdf>
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October 18, 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 proposed changes for its 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, ICER's use of discriminatory methods in its value assessments gives insurers tools to restrict patient access, an unethical tactic that puts the most vulnerable at an increased risk of worse health outcomes, increased out-of-pocket costs associated with their care, and potential adverse events. ICER's value assessments do not promote affordability for patients, but instead give payers justification to create barriers to treatment coverage that benefit their own bottom line. Yet, when patients are treated first with the right treatment for their individual condition, they are more likely to adhere to treatment, become healthier, and holistically save the healthcare system money.

Therefore, we echo our initial comment letter by encouraging ICER to align with innovative leaders in the field of patient engagement and value assessment. When Congress authorized the Patient-Centered Outcomes Research Institute (PCORI), it created a blueprint for engaging patients and people with disabilities throughout the research process to reflect 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. Others in the private sector are following suit to advance patient-centered methodologies for assessing the value of treatments.

With this in mind, we appreciate your considering the following comments on your proposed changes.

ICER continues to defend the use of the QALY and other metrics that treat patients as averages when it should abandon these metrics and focus on development of novel measures of value to account for patient differences and priorities.

In its proposed changes, ICER indicated a commitment to multiple cost-effectiveness outcomes, but remains wedded to the QALY and equal value of life-year gained (evLYG), which treat patients as averages and do not account for heterogeneity in patient populations. We would like to strongly reiterate our criticism of the QALY and reinforce that the evLYG does not sufficiently reform this fundamentally flawed metric.

As we have stated consistently, QALYs discriminate against patients and people with disabilities by placing a lower value on their lives and insufficiently accounting for outcomes that they value. For this reason, the use of QALYs and similar summary metrics of cost-effectiveness have been disallowed for use in our public insurance programs. Medicare is prohibited by law from using a QALY-based threshold to determine coverage, and in 1992 the George H.W. Bush administration determined that state use of a QALY-based system to determine Medicaid coverage would likely violate the Americans with Disabilities Act.

QALYs also fail to properly represent health gain to a heterogeneous patient population. QALY weights are constructed in such a way that inadequately weights quality of life beyond the middle ranges.¹ They are also constructed by a very small subgroup of the country's population² and purport to represent 'all' when they ultimately represent no one.³ Considerable empirical evidence exists to demonstrate that technologies impact people to different degrees and that society strongly disagrees with treating all conditions, disease states, and patient types with the same priority.^{4,5}

This is not merely our perspective – it reflects the viewpoint of the largest analysis of the QALY's underlying assumptions: the European Guidelines for Cost-Effectiveness Assessments of Health Technologies, which concluded that "given the overwhelming methodological limitations of the QALY indicator, and the major inconsistencies which irrefutably invalidate its use, the use of QALY indicators should be abandoned for healthcare decision making."⁶

We would also like to reiterate the point made in our first comment letter on ICER's 2020 Framework that incorporating the evLYG does not resolve the QALY's flaws. 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. A metric based on averages will never adequately reflect patient value, because there is no single perspective on how people see and value health. It is imperative that ICER consider the heterogeneity of patient populations, even within the same condition.

In addition, the evLYG's continued reliance on the QALY for evaluating quality of life improvements poses serious problems. The QALY's flaws are not limited to its underestimating of life-extension. It also fails to account for the full nuance in patient conditions when translating condition-specific measures into utility weights. For example, in ICER's analysis of esketamine,

¹ Smith S, Cano S, Browne J. Patient reported outcome measurement: drawbacks of existing methods. *bmj*. 2019 Feb 27;364:l844.

² McClimans L, Browne JP. Quality of life is a process not an outcome. *Theoretical medicine and bioethics*. 2012 Aug 1;33(4):279-92.

³ Broome J. Fairness versus doing the most good. *The Hastings Center Report*. 1994 Jul 1;24(4):36-9.

⁴ Weinstein MC. A QALY is a QALY is a QALY—or is it? *Journal of health Economics* July 1988 289-291.

⁵ Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *British medical bulletin*. 2010 Dec 1;96(1):5-21.

⁶ Echoutcome. European Guidelines for Cost-Effectiveness Assessments of Health Technologies. 2015, http://echoutcome.eu/images/Echoutcome__Leaflet_Guidelines____final.pdf

a new medication for treatment-resistant depression, ICER translated PHQ-9 scores, a condition-specific measure of depression, into QALY-based utility weights. This translation resulted in considerable lost nuance, since ICER took a measure (the PHQ-9) that ranged from 0 to 27 and simplified it into three health states: no depression, mild/moderate and moderate-severe/severe. As a result, significant improvements in health as measured by the PHQ-9 are assessed by ICER's model as delivering no value to patients due to the reliance on the QALY as the means of value assessment.

Instead of creating another problematic metric, the evLYG, that also does not capture the complexity of patient experience, we urge ICER to fully grasp the limitations of the QALY and invest in condition-specific metrics.

ICER's framework ignores ethical principles with broad support across the general public.

From an ethical perspective, valuing “perfect health” over pre-defined “less than perfect” states of health is fraught with issues. Indeed, our nation's constitutional foundation of equality and our public policies such as the Emergency Medical Treatment and Labor Act (EMTALA), a federal law that requires anyone coming to an emergency department to be stabilized and treated regardless of their insurance status or ability to pay, indicates our ethic to support patients and people with disabilities to maximize their individual potential for health.⁷ To define a life as less valuable because a person's unique circumstances deviate from “average” puts that American ethic at risk. An individual living with a chronic condition may be just as satisfied with their life as another individual with perfect health and should not be afforded less access to treatment.⁸

ICER's QALY-based approach reflects a strict utilitarian mode of thinking that contradicts the traditional American ethic that resources should be allocated to care for people with severe disabilities and chronic illnesses, as well as to research innovations that benefit them. While these groups may represent small portions of the population, the intensity of their need should not reduce their access to lifesaving medical care and reduce investment in research designed to develop innovative new technologies that may improve their outcomes.

Similarly, the QALY-based approach fails to afford patients the opportunity to make their own choices between conflicting priorities or to make tradeoffs. Often, different treatment paths will come with their own distinct benefits and disadvantages (which may manifest differently depending on the patient). The person-centered shared decision-making approach to care desired by most Americans allows patients the choice to select the treatment path most consistent with the values, needs and priorities for care relevant to their own lives. Unfortunately, the use of a QALY-based approach to set coverage decisions and prioritize certain drugs over others within a utilization management framework denies patients that decision-making authority.

⁷ Centers for Medicare & Medicaid Services. (2012, March 26). Emergency Medical Treatment & Labor Act (EMTALA). Retrieved 2017, from <https://www.cms.gov/regulations-and-guidance/legislation/emtala/>

⁸ Pettitt, D., Raza, S., Naughton, B., Roscoe, A., Ramakrishnan, A., Davies, B., . . . Brindley, D. (2016). The Limitations of QALY: A Literature Review. *The Journal of Stem Cell Research & Therapy*, 6(4).

ICER's proposed crosswalk between ICER evidence ratings and the German HTA system is unrealistic and irrelevant.

We question both the relevance and validity of providing a crosswalk between ICER evidence ratings and those of the German health technology assessment (HTA) system. The ICER process is largely a statistical review of evidence from the population perspective. Its evaluation of evidence is primarily based on network meta-analysis, and its sole measure of the quality of evidence is statistical certainty.

By contrast, Germany's Institute for Quality and Efficiency in Health Care (IQWiG) evaluation takes a different approach, which does not as heavily rely on statistical evaluation. Despite key differences between the ICER and IQWiG approaches, both in types of data, methodology, perspective and categorization, ICER believes these two can be simply translated from one to the other. This seems highly unrealistic and ICER does not offer a specific methodology for doing so. It is unclear why ICER is motivated to make this awkward crosswalk.

We support ICER's recognition of the importance of real-world evidence (RWE) and implore it to incorporate RWE in its base models to ensure they carry real-world validity.

We applaud ICER for recognizing the importance of incorporating real world evidence. In the past, there have been numerous occasions in which ICER's estimates of value were significantly flawed due to its over-reliance on randomized clinical trials (RCT) and inappropriate cohort data for estimates of underlying disease burden.⁹

As ICER makes this important change to support and use RWE, we encourage a comprehensive approach to ensure ICER's reports more accurately represent value to the patient. In this spirit, it is essential that RWE is used in actual model input data. Since the aim is to assess the value of a new technology for actual patients in the real world, RWE is clearly a better source than RCTs, which generally include an unrepresentative subtype of young patients without comorbidities or diversity of backgrounds and ethnicities.

It should also be noted that even if ICER does make a committed effort to better incorporate RWE into its models, the value of this effort will be limited if it continues to undertake its reviews so early in the development process; often long before comprehensive RWE is available to be incorporated into models. RWE sources should be prioritized over RCT data for most inputs, including baseline risk, disease burden, cost data, scope, make-up of likely beneficiaries, and health-related quality of life data. If ICER continues to undertake reviews of drugs for which prices and indications are yet to be finalized, during a period when quality of life data are yet to be published, then this effort could be futile, failing to achieve real-world validity in its modeling that can be appropriately translated into a value determination for real people with a disease, chronic condition or disability.

We urge ICER to incorporate patient input meaningfully throughout the entire review process versus the ceremonial nod of summarizing their input.

⁹ Toth PP, Stevens W, Chou JW. Why published studies of the cost-effectiveness of PCSK-9 inhibitors yielded such markedly different results. *Journal of medical economics*. 2017 Jul 3;20(7):749-51.

Though ICER plans to include a separate chapter on the patient experience, we have concerns that this is only a ceremonial nod toward patients versus actually incorporating important patient reported outcomes in the base models of the reports.

If ICER is serious about developing its reports through the patient lens of value, then it should rely on condition-specific preferences of health-related quality of life (HRQOL) versus the QALY in its reports. Furthermore, a summary of patient input in the larger report is insufficient. We would advise that ICER not just summarize the input from patients but share their comments publicly at each stage of the process. Stakeholders have the right to hear directly from patients, not ICER's summation of patients' input. Summarizing lends itself to the omission of items deemed unimportant but may be seminal to patients. Additionally, ICER's summaries do not capture the volume of stakeholders that may have signed one letter related to their views and concerns but represent more than one voice.

We urge ICER to develop a mechanism for incorporating more robust clinician input, particularly when dealing with rare disease populations and want to express concern about the elimination of a higher threshold for treatments for ultra-rare diseases.

One of the biggest challenges facing people with rare diseases in value assessment is the difficulty in developing a research literature for a patient population that may number in the thousands or even hundreds. For such groups, essential information on patient subgroups and variation in medication efficacy and side effects may exist only among clinicians, since the patient population is not large enough to develop a sufficient research literature to meaningfully inform value assessment.

If ICER wishes to offer an honest assessment of value for orphan drugs, they must incorporate clinicians who specialize in serving the patient populations under discussion into the value assessment process.

We also want to express our concern about the elimination of the higher threshold for ultra-rare diseases. There is great need for treatments for rare conditions and disease populations are too small for ICER to evaluate effectively, relying as heavily on RCT data as it currently does. ICER risks limiting access to the populations that need them most based on methodologically flawed reviews. It is also concerning that, based on ICER's description of this change, it is being made solely with the goal of sending a message to manufacturers, not looking out for patients' best interests. ICER states that one of the primary reasons for the change is so that manufacturers do not believe that ICER has formalized \$500,000 per QALY as an appropriate cost-effectiveness threshold for treatments for ultra-rare conditions¹⁰. This stated goal callously overlooks the fact that 95% of rare diseases lack an FDA-approved treatment¹¹. Given that reality, the goal of ensuring that patients are able to access new treatments for these conditions should be prioritized above slapping manufacturers' wrists, and it is concerning that ICER fails to understand this.

¹⁰ Institute for Clinical and Economic Review, 2019. 2020 Value Assessment Framework Proposed Changes. August 21, 2019.

¹¹ Global Genes. Rare Facts. Accessed October 8, 2019.

ICER should allow for appropriate disease specialists and disease-impacted patients to serve as voting members for all reviews.

In order to accurately assess treatments for any condition it is imperative you have clinical specialists in that condition and patients who are living with it at the table.

The diseases for which ICER evaluates treatment are complex and there is a substantial amount of nuance surrounding their treatment. In order to ensure that best practices and the most up-to-date literature for treatment of these diseases is captured, it is imperative to incorporate the views of clinicians who are experts in the disease. As the Headache and Migraine Policy Forum noted in their initial letter on the 2020 Framework, during the 2018 ICER Migraine Review the voting panel initially included an OBGYN as the clinician expert. *After serious concerns were raised by the migraine community, this expert was finally supplanted by a neurologist.* Medical students typically undergo one hour of education on all topics related to neurology, which is an insufficient amount of training to fully understand the content of the review. This is one example of a pervasive problem within ICER reviews. In order to truly understand the nuance of a disease and its treatment ICER must include clinicians that are experts in the disease state.

ICER also consistently overlooks outcomes that matter to patients, such as respiratory function in the Duchenne Muscular Dystrophy Assessment. By incorporating patients as equal voting members, ICER would ensure that outcomes that truly matter to patients are being factored into their overall assessments.

We support ICER's decision to re-evaluate evidence one year after each final report, but we continue to implore ICER to set more stringent standards for minimum data requirements for reviews and to cease conducting harmful premature reviews.

We continue to urge ICER to cease conducting premature reports and to wait until adequate data is available to produce more accurate and scientifically rigorous reports. ICER notes that "... (ICER) strongly believe(s) that such value assessments need to be conducted around the time of launch, to allow policymakers to make coverage and treatment decisions based on the best information available at the time."

This statement relies on the assumption that inadequate data is more helpful or more informative than no data at all. Having significant numbers of insurers or providers limit access to new technologies due to flawed or incomplete data on value will impose costs in terms of the delayed health gains to patients.¹² Currently, ICER sees itself as the protector of the healthcare purse, providing payers flawed information to excuse restricted coverage at the expense of patients and people with disabilities. There must be a strong case for delaying access to new medicines, not just a justification not to spend, and it must be based on the best data available. It is inhumane and unethical for ICER to take the stance that we must save money first and overturn decisions on restricting access only when value has been proven, while patients suffer in the interim.

¹² Stevens W, Philipson T, Wu Y, Chen C, Lakdawalla D. A cost-benefit analysis of using evidence of effectiveness in terms of progression free survival in making reimbursement decisions on new cancer therapies. Forum for Health Economics and Policy 2014 Jan 1 (Vol. 17, No. 1, pp. 21-52).

Expanding on this, given ICER's practice of undertaking many of its reviews far too early - often when there is inadequate data available to make realistic estimates of value - we agree with and support ICER's proposal to re-evaluate evidence one year after the release of each final report. The existence of time-variance as a driver in cost-effectiveness is very much an issue that is being discussed in academic circles. We would hope, given the prematurity of many of ICER's initial reports, that ICER puts as much emphasis on its newer results and updates to initial reports as it does to its primary report launches. Later reports will likely be more accurate than the early reports and should be emphasized.

ICER has chosen to give itself eight more weeks for large class reviews while passing a one week extension on to patients. If ICER actually values meaningful input from stakeholders, especially patients, comment periods must be extended.

Over the years ICER has heard from the Partnership to Improve Patient Care and many other patient groups that they allow insufficient comment periods. Advocacy organizations have tremendous depth of knowledge and information to share on the real-world value of treatments, yet often have few resources to dedicate to ICER's process. Meaningful patient engagement requires longer comment periods for patients to develop thoughtful and substantive input. Though ICER has proposed elongating its timeline by nine weeks for large class reviews, only *one* of those weeks is being added to the comment period. This follows ICER's concerning pattern of short-changing the patient voice by not allowing time and resources for patient advocates to fully engage. If ICER is serious about valuing patient input, extensions should be granted to both comment periods equivalent to the time extension ICER is giving itself.

As ICER looks to apply more precise evidence ratings, it is imperative that this is implemented in a manner that reflects a real-world setting and heterogeneous patient population.

External validity should be ICER's primary focus in cost-effectiveness analyses. ICER cannot improve upon the internal validity of a clinical trial *ex ante*, so its sole purpose is to ensure that such evidence can be applied with relevance to a wider audience. ICER's reports seek to instruct general medical practice and policy in a world where there is no 'controlling' of selection of subject.^{13, 14}

Given the clear difference in importance of internal and external validity for producing value assessments, we would suggest that evidence ratings be undertaken separately for both internal and external validity and also extend beyond simple 'effectiveness' to other sources of input data used in comparative effectiveness models such as cost data, real world burden, real world risk, transition probabilities between health states, and quality of life data.

¹³ Glasgow RE, Green LW, Klesges LM, Abrams DB, Fisher EB, Goldstein MG, Hayman LL, Ockene JK, Tracy Orleans C. External validity: we need to do more. *Annals of Behavioral Medicine*. 2006 Apr 1;31(2):105-8.

¹⁴ Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn 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.

We would also suggest implementing evidence ratings of effectiveness that concentrate not just on selection bias, uncertainty and reliability but also measures of heterogeneity. Although ICER states clearly in this document that it takes a ‘population’ perspective to evidence (lines 360-373), we strongly recommend that ICER also acknowledge that the average does not represent all.

In ICER’s published assessments, the issue of heterogeneity has not been featured strongly in the reports of the main clinical results. In its cost-effectiveness analyses, heterogeneity is only addressed post-hoc after the main model has been built. ICER’s Evidence Rating Matrix makes no mention of whether a study attempts to detect or understand heterogeneity or to report results by subgroup. It is imperative that ICER recognize the importance of evidence on heterogeneity as it has been well established that reporting of differential value assessment across subgroups will lead to substantial health gains, both through treatment selection and coverage.^{15, 16, 17}

ICER states that when dealing with particular individuals, “*decisions will be made with other sources of data in mind.*” The problem is that with increasing evidence of genetic and epigenetic impacts on relative effectiveness of different therapies as well as the growing importance of personalized medicine in the health care industry, ignoring heterogeneity will result in providing evidence that is relevant for no one, rather than relevant for everyone.

Conclusion

Thank you for your consideration of our suggestions on ways in which ICER can make its value assessments fair and equitable to patients. Please feel free to reach out to Sara van Geertruyden (sara@pipcpatients.org) in response to our recommendations above.

Sincerely,

ACCSES
Aimed Alliance
Alliance for Aging Research
Alstrom Syndrome International
American Association on Health and Disability
American Autoimmune Related Diseases Association
Association of Migraine Disorders
Association of University Centers on Disabilities
Asthma and Allergy Foundation of America
Beyond Type 1
Bridge the Gap -Syngap – Education and Research Foundation

¹⁵ 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.

¹⁶ Basu A, Jena A, Philipson T. Impact of comparative effectiveness research on health and healthcare spending. *Journal of Health Economics* 2011; 30(4): 695-706.

¹⁷ 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.

CancerCare
CARE About Fibroids
ClusterBusters
Cystic Fibrosis Research, Inc. (CFRI)
Diabetes Patient Advocacy Coalition
Epilepsy Foundation
Epilepsy Foundation New England
Genetic Alliance
Global Healthy Living Foundation
Global Liver Institute
GO2 Foundation for Lung Cancer
GoldenGraine
Heart Valve Voice US
Hope for Migraine Community
Institute for Patient Access
International Foundation for Autoimmune & Autoinflammatory Arthritis
Lakeshore Foundation
Lupus and Allied Diseases Association, Inc.
LymeDisease.org
Men's Health Network
Mended Hearts
Miles for Migraine
MLD Foundation
National Alliance on Mental Illness
National Diabetes Volunteer Leadership Council
National Headache Foundation
National Infusion Center Association
Not Dead Yet
Partnership to Improve Patient Care
Preventive Cardiovascular Nurses Association
PXE International
Rosie Bartel
Sick Cells
SoldierStrong Access
The Bonnell Foundation: Living with Cystic Fibrosis
The Coalition For Headache and Migraine Patients
The Headache and Migraine Policy Forum
The Migraine Diva
Tuberous Sclerosis Alliance
U.S. Pain Foundation
United Spinal Association



October 18, 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: Proposed Updates to the 2020 Value Assessment Framework Methods and Procedures

Dear Dr. Pearson:

The Personalized Medicine Coalition (PMC) appreciates the opportunity to submit comments regarding the proposed updates to the Institute for Clinical and Economic Review (ICER)'s 2020 value assessment framework methods and procedures, to be finalized in December 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 evolving 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 comments on the updates to ICER's value assessment framework, herein called the framework, are focused exclusively on the extent to which the proposed changes 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. Treatment strategies that are targeted based on a patient's molecular characteristics and individual circumstances improve outcomes by allowing physicians to know which treatments may be more effective and safer to use for each patient. 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.

PMC welcomed the opportunity to provide broad comments to ICER regarding the 2020 framework on June 10, 2019. As reflected in our earlier comments, the framework would benefit from a greater consideration of personalized medicine within its objectives, methods and procedures.

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To this end, PMC recommends that ICER recognize five principles related to personalized medicine as it considers the updated framework. These principles represent the foundation on which our general comments and our comments regarding specific proposed updates are based.

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 insights on emerging or evolving value elements over time.
4. Valuation approaches should be transparent and consistent; should include a broad array of benefits that are important to patients and society; and should adequately account for population diversity through consideration of patient heterogeneity.
5. All stakeholders must be engaged, and multiple perspectives must be integrated throughout the value assessment process.

A Statement on the Intended Purpose of This Letter

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 methods and procedures.

General Comments Regarding the Framework

As we stated on June 10, 2019, in our comments on broad changes needed to the framework, we offer these general comments about how the scope of the framework may affect the field of personalized medicine. 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).

The Population Perspective and Heterogeneity

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, the negative consequences these assessments may have on patient access. A population-level framework may encourage the restriction of access to a new drug based on reported averages, which limits treatment options available to individual patients who may have benefitted from them.

Furthermore, by focusing on evaluating the overall average effectiveness, the framework doesn't encourage the generation of useful evidence on heterogeneity that can inform differential decisions about the extent to which individuals or subgroups may benefit from new health care technologies.

In ICER's published assessments, heterogeneity has not been featured strongly in the reports of the main clinical results, and in cost-effectiveness analyses heterogeneity has only been addressed post-hoc after the main model has been built. ICER's Evidence Rating Matrix does not focus on understanding heterogeneity or report results by subgroup. It is imperative that ICER recognizes the importance of evidence on heterogeneity, as it has been well established that reporting of differential value assessment across subgroups will lead to substantial health gains, both through treatment selection and coverage (Basu A. Estimating person-centered treatment (Pet) effects using instrumental variables: an application to evaluating prostate cancer treatments. *Journal of Applied Econometrics*. 2014 Jun;29(4):671-91; 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; Kreif N, Grieve R, Radice R, Sadique Z, Ramsahai R, Sekhon JS. Methods for estimating subgroup effects in cost-effectiveness analyses that use observational data. *Medical Decision Making*. 2012 Nov;32(6):750-63).

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 preferences; 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.

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 the 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.

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 also 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 most effective treatment to a patient, but also avoiding the use of treatments that will not work in some patients), 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.

Alternative Value Assessment Framework Considerations for Rare Diseases

Not all conditions for which the value of treatments may be assessed are subject to the same set of weighted value factors. For example, standard assessment processes frequently fail to account for the unique characteristics of innovative therapies for rare diseases. Collecting clinical data in patient populations with rare diseases is challenging for many reasons, including: a limited knowledge of disease history and its progression; the fact that many of these conditions frequently affect particularly vulnerable groups such as children and are not associated with any established therapies; and the complications associated with trial results that are frequently associated with much greater uncertainty due to small numbers of patients. Rare disease treatments are further disadvantaged because standard value assessment methodologies are typically designed for more prevalent conditions with relatively lower incremental costs. PMC recommends that ICER develop alternative value assessment framework strategies for differing types of conditions such as rare and ultra-rare conditions that take into account the unique characteristics of these situations and their value to society. For example, ICER could take advantage of observational data, such as that coming from RWE sources like EHRs, registries, and natural history studies in the evaluation of treatments for rare diseases. However, until such time as alternative value assessment strategies can be put in place following solicitation of stakeholder comments, PMC recommends that ICER hold off on value assessments for innovative treatments for rare and ultra-rare conditions.

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. But 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, and it is impractical to be able to fully react to and respond to ICER's complex and lengthy reports in a short period of time. PMC also reiterates its recommendation that all comments submitted to ICER 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.

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 emphasize and detail the patient-provided information that would be valuable for patient groups to collect. In addition, we recommend that ICER further expand the questionnaire to explicitly include separate questions for "each value element" prioritized by patients, caregivers, and providers during ICER's engagements on topics. Patient groups will be better able to accommodate requests and provide high-quality data the sooner they are made aware of a call for feedback and of what types of input/data collection will be useful.

Comments Regarding Specific Areas for Which ICER is Requesting Input

We appreciate ICER's call for comments on proposed updates to 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.

1. Augmenting efforts to use 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. RCTs have great value in determining the clinical safety and efficacy of therapies in optimal settings, but value

can differ in clinical settings due to variation in physician practices. RCT data is often very homogenous due to inclusion/exclusion criteria of trial participants; however, value assessments are meant to draw conclusions for the wider population. RWE, by contrast, provides evidence that is more relevant to a diverse population and can reveal when there are advantages for particular sets of patients. 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 assessing the value of personalized medicine strategies. The proposed updates to the 2020 framework, including a process for formal request of stakeholders who are engaging on a review project to submit relevant RWE, and the exploration of opportunities with third party organizations to provide RWE, do not go far enough. 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. RWE can also provide insight into "current" treatment patterns and standards of care, given that trials are typically conducted a number of years before a product's launch and the appropriate comparator may have changed since that time. 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.

The Food and Drug Administration is exploring the use of RWE in efficacy determinations and has a long history of its use in post-market surveillance processes. While ICER should continue to adapt methods for the routine use of RWE in evaluation processes, in these cases, any RWE generated for FDA review should be taken into consideration in ICER evaluations. In addition, it is worth noting that RWE is being used by international and European health technology assessment bodies as an alternative source of comparative evidence when RCTs are not feasible, or when evidence from RCTs is inadequate.

As part of the proposed updates, it is stated that ICER will explore collaborative relationships with organizations that may serve as sources of real-world data (RWD). There are risks associated with using third party organizations to generate and report RWD for use in value assessments, including potential bias and non-disclosed incentives to generate inefficient data. ICER should develop safeguards against these potential risks. Furthermore, RCT data is subject to quality standards, including "fit for use", which is needed to assure quality evidence for evaluation purposes. RWE should have a similar set of standards to assure quality and applicability of this data type.

Furthermore, through this process, ICER has proposed that it generate RWD to complement published data sources during its value assessments. Given the timing of ICER's assessments, it is unlikely that ICER or real-world studies developed by third parties would be afforded the rigors of scientific peer-review prior to inclusion as inputs in ICER's assessments. We therefore encourage ICER to thoughtfully consider methodologic and process guidelines for RWE developed by the Joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) Special Task Force on RWE (Berger 2017), including recommendations for stakeholder (e.g., patient, manufacturer) consultation and public study registration and publication.

2. *Capturing other important potential benefits and contextual considerations.*

As part of the proposed updates, ICER has made no significant proposals to the base methodology through which additional dimensions of value would receive a quantified weighting. The proposed updates include, however, the addition of dimensions of value as new categories of "other potential benefits or disadvantages"

within assessments of single dose transformative therapies for appraisal by a voting panel. Voting panels, however, may not have the expertise to evaluate value factors in a meaningful way. Many “contextual considerations” can and will have a significant effect on the value of a treatment. ICER’s approach is therefore insufficient and does not quantitatively incorporate the impact of many important patient-centered factors.

One example of an overlooked factor related to personalized medicine is the consideration of diagnostic testing to help drive treatment safety, efficacy, and efficiency. 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.” 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 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 the value of novel drugs.

Other important value factors further reflect heterogeneity, patient preferences, health care delivery management, and other factors related to individual patient characteristics and care. These must be formally accounted for in value assessment methodologies where possible. While there is no standard methodology in place for quantitatively incorporating these patient-centered factors into assessment results, they will nonetheless play a significant role in the overall value of any treatment. It is critical that newly developed methodologies, such as multi-decision criteria analysis and bayesian network modeling be further developed and tested.

3. Multiple cost-effectiveness outcome measures.

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.

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, multi-faceted 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. Including the complementary equal value of life years gained (evLYG) measure in assessment methodologies is a step in the right direction, but this measure is also limited. A single measure, such as the QALY, cannot adequately capture true patient-centered value and the broad heterogeneity of clinically relevant characteristics and preferences across patients and diseases. While adding the evLYG measure brings additional considerations into the assessment, it is still reliant on the QALY and therefore not an independent measure. Both metrics are based on averages. It is imperative that ICER consider the heterogeneity of patient populations, even within the same condition. PMC therefore recommends disaggregating the QALY-based metrics and considering a more comprehensive set of value elements that is inclusive and reflects patient heterogeneity as well as personalized medicine services and concepts.

4. Cost-effectiveness thresholds.

The proposed updates to the framework involve the implementation of a range of incremental cost-effectiveness thresholds and value-based price benchmarks, 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. No threshold range 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 care strategies that are cheap in the short-term but inefficient over time, thereby moving away from personalized medicine and reducing the value of our health care dollar.

5. New processes for re-evaluating evidence.

The proposed updates include revised re-evaluation timelines, pointing to reassessments one year after the publication of a report. PMC applauds ICER for considering re-evaluation sooner than the two-year period previously employed; however, the timeframe should be less arbitrary and more explicitly tied to new and evolving evidence regarding a given treatment. Arbitrary timelines for consideration of evidence to trigger a re-evaluation assumes that information will become available at a single point in time. Evidence, however, continuously accumulates over time.

The personalized medicine field is evolving too rapidly to accurately maintain a current assessment of treatment value with a single static period between assessment review and associated 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 considered for updating 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. Additionally, PMC recommends that ICER provide a mechanism for external stakeholders to request re-evaluation when new data emerges.

7. Evidence ratings.

While ICER has proposed an expansion of evidence rating categories, the methods still do not adequately reflect the relative contribution to the overall long-term value of contextual considerations, and other benefits and disadvantages. The impact of these considerations remains subjective. For example, the consideration of predictive diagnostic testing results can considerably reduce uncertainty related to treatment safety and efficacy in some cases. However, ICER's current approach leaves the consideration of these factors up to the discretion of a 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 heterogeneity considerations.

Relying on subjective contextual considerations risks applying false weight and a false sense of precision and accuracy to these important value elements. Many evidence ratings would simply not address the complexity

within a diverse population. ICER's evidence ratings may therefore undervalue innovative personalized medicines, as it may be particularly problematic for newer treatments and therapies where evidence of sub-population benefits may not be considered at the time of assessment.

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 and assures that emerging evidence of patient heterogeneity is appropriately considered in evaluations.

Evidence ratings should concentrate not just on selection bias, uncertainty, and reliability but also measures of heterogeneity. ICER states that when dealing with particular individuals, "decisions will be made with other sources of data in mind." However, with increased evidence of genetic and epigenetic factors on the relative effectiveness of different therapies as well as the growing importance of personalized medicines in the health care industry, an evidence rating system that does not consistently factor in heterogeneity will have limited relevance.

8. Crosswalk between ICER evidence ratings and those of the German health technology assessment system.

As part of the proposed updated to the 2020 framework, ICER would introduce evidence ratings designed to crosswalk to the German Institute for Quality and Efficiency in Health Care (IQWiG) evaluation approach. The IQWiG system, which utilizes distinct methodologies and assumptions, can provide valuable conceptual considerations for ICER as it evolves its assessment methodologies, but a direct crosswalk comparison could be misleading as it might lead to a false impression that the two outputs are coordinated and relevant to one another in all settings. For example, the IQWiG system may have better processes to contend with differing value parameters related to different conditions such as rare and ultra-rare diseases, and these processes should be examined to determine how they can be implemented into ICER's methodologies. These processes, however, should be put into context as related to the current ICER evaluation system, which is ill-equipped to account for differing condition-specific value parameters. Such a comparison could create an opportunity for misuse of assessment measures to undermine the underlying value parameters associated with IQWiG evaluations.

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 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:

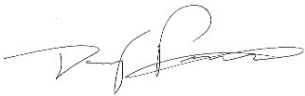
1. Considerations related to personalized medicine, such as heterogeneity of treatment effect, treatment efficiency (i.e., potential cost savings by avoiding less effective treatment or adverse side effects), and individual values and circumstances can significantly impact comparative clinical effectiveness 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, include a broad array of benefits that are important to patients and society, and adequately account for population diversity through consideration of patient heterogeneity.
5. All stakeholders must be engaged, and multiple perspectives must be integrated throughout the value assessment process.

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 valuable technologies that are safe and effective and 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 PMC at dpritchard@personalizedmedicinecoalition.org or 202-787-5912. We look forward to further opportunities to provide feedback.

Sincerely,



Daryl Pritchard
Senior Vice President, Science Policy
Personalized Medicine Coalition



October 18, 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: 2020 Value Assessment Framework Proposed Changes

Dear Dr. Pearson:

Spark Therapeutics ("Spark") is pleased to submit comments on the Institute for Clinical and Economic Review's (ICER) "2020 Value Assessment Framework Proposed Changes" ("Proposed Changes"). Although we appreciate the opportunity ICER has provided to weigh-in on their value assessment framework, the proposed changes seem at odds with its mission and the needs of the stakeholders relying on ICER's evidence reports.

ICER describes itself as "an independent and non-partisan research organization that objectively evaluates the clinical and economic value of prescription drugs, medical tests, and other health care and health care delivery innovations." Furthermore, it claims to "include a full analysis of how well each new drug works, the economic value each treatment represents, and other elements of value that are important to patients and their families."¹

If ICER wishes to provide an objective evaluation and a full analysis of the value of prescription drugs, it should also be committed to transparency. The latest iteration of ICER's value framework has shown that ICER is instead choosing to limit the information available in its reports. In particular, there are a number of suggestions from stakeholders that were not considered or changed from previous drafts that would provide more information to interested parties. These include the threshold values for ultra-rare diseases, discounting practices, and including the societal perspective in ICER analyses. We focus on these issues in our comments because we feel strongly that the framework should provide all stakeholders with the information they need to make informed decisions, irrespective of how ICER wants or thinks those results to be interpreted.

Threshold values for ultra-rare diseases

ICER has proposed that "[i]n all reports, ICER will provide a set of results using standardized cost-effectiveness thresholds from \$50,000-\$200,000 per quality adjusted life year (QALY) and per equal value of life years gained (evLYG). ICER will provide cost-per-QALY results at \$50,000, \$100,000, \$150,000 and \$200,000 per QALY and per evLYG for all assessments, including those for treatments of ultra-rare

¹ ICER Website: <https://icer-review.org/about/>

disorders.”² Without stating it formally, ICER is removing the evaluation of cost-effectiveness at two thresholds they have previously provided, \$300,000 and \$500,000 per QALY. We think eliminating these threshold values is removing information that may be important to payers and patients and should be included in ICER reports.

ICER has a few justifications for the removal of these thresholds. It argues that even ultra-orphan therapies can have blockbuster sales, using the hypothetical example of a therapy with a \$100,000 price being administered to 10,000 individuals. However, that is certainly not the norm for ultra-orphan products. Beyond the fact that a company’s profits are not a part of the assessment of value of a particular product, the reality is that the majority of ultra-orphan therapies are only administered to patient populations in the hundreds if not fewer.³

Moreover, ICER argues that there are equity concerns in including higher thresholds in the evaluation of ultra-orphan diseases. This statement, however, does not reflect research on the societal preferences; there is strong correlation between rarity and unmet need⁴, and studies of societal preferences consistently find a preference for prioritizing diseases with severe unmet need.⁵ This is precisely why both health-technology assessment bodies in England and the Netherlands, (The National Institute for Health and Care Excellence (NICE) and Zorginstituut Nederland (ZiN)) have taken steps to weight QALY gains by adjusting cost-per-QALY threshold for magnitude of incremental QALY gains and for disease severity, respectively.⁶ As we have commented previously, NICE’s proposed approach to QALY weighting for ultra-orphan diseases involves use of an incremental cost-per-QALY threshold ranging from 5 to 10 times the standard level.⁷ Applying such adjustments to ICER’s standard thresholds, for example value-based-price

² ICER. “2020 Value Assessment Proposed Changes.” 2019; p. 14. Available at: https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_VAF_Proposals_082119-1.pdf

³ “Figures 2-1A-D show the distribution of rare conditions according to prevalence as presented in the Orphanet report. They reveal an overall distribution that is highly skewed to very rare conditions. In fact, data for approximately 1,400 of the approximately 2,000 conditions (about 70 percent) consist only of case reports for individuals or families.” (See Boat TF, Field MJ. Rare diseases and orphan products: Accelerating research and development: National Academies Press; 2011).

⁴ Rodriguez-Monguio R, et al. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients’ health needs? 2017. Orphanet Journal of Rare Diseases;12:1.

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⁶ Raftery J. NICE’s proposed new QALY modifier for appraising highly specialised technologies The BMJ Opinion2017 [updated 18 April 2017]. Available from: <http://blogs.bmj.com/bmj/2017/04/18/nices-proposed-new-qaly-modifier-for-appraising-highly-specialised-technologies/>.

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Zwaap J, Knies S, van der Meijden C, Staal P, van der Heiden L. Cost-effectiveness in practice. Zorginstituut Nederlands; 2015 26 June 2015.

⁷ 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

benchmarks of \$100,000 - \$150,000, would suggest use of a range of \$500,000 - \$1,500,000, well above the range used by ICER previously in its assessment of ultra-orphan therapies and even more so given the most recent proposed changes.

Finally, including cost-effectiveness levels at higher thresholds for ultra-orphans is not an endorsement of those higher thresholds but is important in providing more complete information to payers. If ICER feels strongly that payers should be cautious about funding therapies that are only cost-effective at those higher thresholds, then adding wording to the “Controversies and Uncertainties” section of its reports is more appropriate, not the complete removal of these sensitivity analyses.

Discounting

In its explanation on the proposed changes ICER states, “[w]e also do not propose presenting sensitivity analyses that vary the discount rate, as we do not believe this would provide additional information that is useful to decision-makers in this context.”⁸ However, this argument does not ring true in the case of Single or Short-Term Transformative Therapies (SSTs). As we noted in our recent comments on the proposed adaptations for SSTs, showing both discounted and undiscounted results is not without precedent. Calculation of discounted and undiscounted QALYs, costs and incremental cost effectiveness ratios (ICERs) is recommended by other well-known health technology assessment review processes including the one by England’s NICE when results are sensitive to different rates.⁹ In fact, ICER’s previously published 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.¹⁰

Once again, the provision of information in ICER reports is not the same as saying that the results stemming from it are the ones that should be relied upon for decision-making. Rather, it provides greater transparency to payers and patients about whether discounting greatly impacts the final “takeaway,” allowing them to make decisions accordingly. This is particularly important with one-time therapies entering the market where costs are typically upfront, but benefits are accrued over a lifetime. We feel strongly that this level of transparency in reporting results is vital for patients, payers, and other interested stakeholders to better understand the impact of discounting on whether a therapy is considered cost-effective.

Societal perspective

A major stated purpose of ICER’s reports is to provide payers (government and private) information on a therapies value so that payers can make informed decisions on access and coverage. A number of indirect costs such as productivity and work loss are quite relevant and important to private payers. In the case of

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).

⁸ ICER. “2020 Value Assessment Proposed Changes.” 2019; p. 21. Available at: https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_VAF_Proposals_082119-1.pdf

⁹ “For the reference case an annual discount rate of 3.5% should be used for both costs and benefits. When results are potentially sensitive to the discount rate used, consideration should be given to sensitivity analyses that use differential rates for costs and outcomes and/or that vary the rate between 0% and 6% (see NICE, “Discounting of health benefits in special circumstances.” Available at: <https://www.nice.org.uk/guidance/ta235/resources/osteosarcoma-mifamurtide-discounting-of-health-benefits-in-special-circumstances2>.)”

¹⁰ 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.

government payers, broader wellbeing of society as well as implications for other government programs and tax revenue are also relevant to their decisions on funding. Given the importance of indirect costs, the societal perspective reported by ICER should not be buried within their final evidence reports. Rather, it should be shown alongside the payer perspective and ideally part of their press release and Report-at-a-Glance. In situations where the societal perspective is similar to the payer perspective, the reporting of this information will only go further to support ICER's payer analysis. In the case where the results diverge, highlighting both will provide valuable information to payers in a clear and easy to access manner.

Conclusion

Spark believes it is imperative that the final evidence reports published by ICER provide a clear and transparent view of the long-term value of a therapy. The current Proposed Changes seem to be a movement away from that goal. ICER has the ability to indicate what it believes is the appropriate analysis to rely upon; the addition of various sensitivity analyses do not detract from that conclusion. We strongly urge ICER to consider our concerns and recommendations as transparency is an important tenant for any agency providing information that could influence patient access to vital therapeutic options. This is particularly true for therapies that address high unmet need for ultra-orphan diseases or are innovative and potentially curative.

As always, please do not hesitate to contact me at sarah.pitluck@sparktx.com or 202-431-6706 with any questions about our comments.

Sincerely,

A handwritten signature in blue ink, appearing to read 'Sarah Pitluck', with a stylized flourish at the end.

Sarah Pitluck
Head, Global Pricing & Reimbursement

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October 18, 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

Re: ICER Proposed Changes to its 2020 Value Assessment
Framework

Dear Dr. Pearson:

The Society for Women's Health Research (SWHR) appreciates the opportunity to provide public comment on proposed changes to the Institute for Clinical and Economic Review (ICER) 2020 value assessment framework. SWHR is a nearly 30-year-old education and advocacy nonprofit dedicated to promoting research on biological sex differences and improving women's health through science, policy, and education. We are uniquely positioned to serve as a resource to ICER on key aspects of value assessment that have implications for women and their health.

SWHR's open input comments from June 10 offered practical information and suggestions on how ICER can improve the methods it uses to assess the value of drugs and health care interventions and the processes it follows to engage with stakeholders. On October 11, we shared with ICER a set of principles that SWHR conceived to help ensure that value frameworks and assessments, including those of ICER, reflect factors relevant to women and the ongoing improvement of their health, as well as allow for access to new therapies.

While we are encouraged that ICER's proposed updates released on August 21 provide some incremental improvements that align with SWHR principles, the changes do not go far enough to support optimal health outcomes for women as patients, caregivers, and health care decision-makers for themselves and their families. As previously stated

in our June 10 open input letter and in SWHR's Health Care Value Assessment Principles, women's roles in health care are complex and multifaceted. Therefore, the framework should be designed to incorporate specific challenges faced by individuals interacting with the health care system from a variety of perspectives.

- 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 appreciates this opportunity to provide recommendations and feedback in response to ICER's proposed value framework.

Section 1.2 (Population Perspective and Intended Uses)

SWHR Recommendation 1: Consider and account for population differences (including sex and gender) to inform what is or is not known about the variation in response to different treatments.

ICER states that one important goal of its value framework is “to provide an evidence report that does a better job of analyzing the strengths and limitations of the available evidence, including what is or is not known about the variation in response to different treatments among patients with different personal and clinical characteristics” [lines 368-371].

As discussed in SWHR's June 10 comments, sex and gender play critical roles in the risk, pathophysiology, presentation, diagnosis, treatment, and management of disease.

- 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

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.⁶ ICER should consider and account for population differences including sex and gender in its value framework to inform what is or is not known about variation in response to different treatments.

Section 3.1 (Sources of Evidence)

SWHR Recommendation 2a: Use a broad range of high-quality, real-world evidence sources.

SWHR is pleased that ICER reaffirmed its commitment to using existing real-world evidence (RWE) for future reviews. RWE is clinical evidence derived from analysis of real-world data (RWD) about the usage and potential benefits or risks of a medical product.⁷

As discussed in our June 10 comments, 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.

Although RWE will not be available for new drugs at launch, it may be available for marketed products, making it potentially useful for therapeutic class reviews as well as updated reviews. Importantly, RWE may provide important information to assess whether outcomes differ by sex and gender.

SWHR Recommendation 2b: Articulate ICER principles and methods for incorporating RWE into future topic reviews, including discussion of when RWE may be discarded.

In Section 3.1, ICER states that “as with all evidence, ICER will assess the internal and external validity of RWE as part of a larger judgment of whether and how that evidence should be incorporated in an assessment. As part of this broad commitment, ICER will continue to formally request that stakeholders who are engaging on a review project submit relevant RWE for consideration in the evidence review” [lines 389-393].

As SWHR suggested in our June comments, ICER should articulate not only overarching principles but corresponding systematic methods for evaluating RWE in future topic reviews, including discussion of instances where ICER may discard RWE in favor of exclusive use of randomized clinical trials (RCTs). ICER should leverage existing resources, information, and best practices from experts in the field instead of initiating *de novo* work in this area. A few examples are:

- 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 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.
- In September 2019, the Duke-Margolis Center for Health Policy released [Determining Real-World Data's Fitness for Use and the Role of Reliability](#), a new white paper that outlines a framework for how researchers and reviewers can systematically evaluate whether RWD are fit for use by using verification checks to assess reliability. This paper

aims to serve as a resource for sponsors in designing studies using RWD sources, for regulators in developing policy, and for researchers in developing study methodology best practices.

SWHR Recommendation 2c: Outline ICER process for generating and analyzing new RWE with potential collaborators.

In Section 3.1, ICER also states that it “*will seek opportunities to generate new RWE for incorporation in reviews. ICER will explore collaborative relationships with organizations that may serve as sources of real-world data in order to generate RWE during reviews that can complement published data sources*” [lines 395-397].

SWHR supports the concept of ICER working collaboratively with organizations that may serve as sources of RWD and/or have expertise in analyzing RWE that could be leveraged for new analyses. ICER provides limited details, however, regarding a) the process it will undertake to identify potential RWE partners and b) the methods it will use to make judgments about whether RWE analyses will “*address key gaps in the evidence base and be feasible within the timeframes of an ICER review*” [lines 423-424].

SWHR urges ICER to proceed thoughtfully in developing its vision, methods, and process for generating new RWE for use in its assessments. ICER’s historical role has been to evaluate evidence, not generate it. Therefore, we ask that ICER clarify its own role, capability, and capacity to perform *de novo* RWD/RWE studies. We also encourage ICER to outline a well-articulated process for working with organizations to leverage their expertise in generating and analyzing RWE to develop and test best practices for determining when and how RWE should be incorporated into future topic reviews.

Section 3.3 (Cross-Reference with German Evidence Ratings)

SWHR Recommendation 3: Drop new proposal to cross-reference with German evidence ratings.

ICER introduces a new proposal to “*provide complementary evidence ratings using the German categories of ‘added benefit’*” [lines 470-471]. In addition to its own evidence ratings, ICER “*will seek to translate its judgment of the evidence into the rating system for added clinical benefit used in Germany to summary drug assessments and guide pricing considerations*” [lines 471-473].

Interest and use of ICER’s work in other pharmaceutical markets should not be a catalyst for ICER to translate evidence using its “*own judgment of ‘added benefit’ within the German categories to complement ICER’s own methods*” [lines 485-486]. ICER’s use of a “*rough algorithm for the crosswalk between the two systems*” [lines 516-517] that relies on ICER’s own judgement is concerning because it is inconsistent with ICER’s stated charter to objectively

evaluate the clinical and economic value of health care innovations.⁸ SWHR recommends ICER reconsider this proposal and drop the cross-reference with German Evidence Ratings from its 2020 value assessment framework update.

Section 3.4 (Base-Case Perspective in Economic Models)

SWHR Recommendation 4: Include societal perspective as a base case in cost-effectiveness models.

While ICER currently conducts cost-effectiveness analyses (CEA) from both the health care sector and societal perspectives, it “*chooses to use the health system perspective as the basis for its primary base-case results*” [lines 857-859]. Excluding relevant costs outside of those incurred by the health care sector (i.e., insurance or a national payer) obscures critical cost savings that capture the comprehensive value of a new intervention/therapy.

SWHR urges ICER to include the societal perspective as an additional base case of CEA for future reviews to ensure that factors important to women such as productivity and caregiver burden are reflected in ICER value-based price benchmarking for a technology/therapy. Use of the societal perspective is an established health economics methodology that is recommended by the Second Panel on Cost-Effectiveness in Health and Medicine, a nonfederal panel with expertise in CEA, clinical medicine, ethics, and health outcomes measurement convened by the U.S. Public Health Service (PHS).⁹ ICER should include societal base-case results in all of its reports and summaries (i.e., press results and report-at-a-glance documents).

Section 3.6. (Alternative Economic Model Assumptions)

SWHR Recommendation 5a: Increase subgroup analyses to capture patient heterogeneity.

SWHR Recommendation 5b: Incorporate subgroup value metrics to quantify treatment option optimization among patient populations more narrowly.

SWHR is encouraged that ICER will “*include scenarios with different patient subgroups to account for the heterogeneity within patient groups within a specific disease area*” [lines 1067-1068]. SWHR’s June comments discussed the need for ICER methods to incorporate patient subgroup outcomes and treatment preferences into its value framework. As discussed in Section 1.2 (Population Perspective and Intended Uses), this is necessary to understand 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.

SWHR Recommendation 6: Quantitatively account for a broad array of patient and societal factors to reflect a treatment's value comprehensively.

Value assessment frameworks should account for what matters most to patients, caregivers, and society, in addition to measuring clinical outcomes. To provide a comprehensive snapshot of a treatment's value, a broad array of factors should be considered and quantitatively accounted for in value assessment cost-effective methodologies.

As outlined in SWHR Health Care Value Assessment Principle #3 and our June comments, burden of illness factors that are important to women include (but are not limited to):

- Survival
- Ability to function/work
 - Presenteeism
 - Absenteeism
 - Employment disability
- Quality of life
 - Physical and social well-being
 - Pain or discomfort
- Levels of disease burden and progression
- Comorbid conditions or concomitant medications
- Caregiver burden¹⁰
 - Permanent difficulty, stress, or negative experiences resulting from providing care¹¹
 - Physical, emotional, and financial cost of the caregiving
- Limitations in treatment
 - None (i.e., a treatment does not exist for a particular condition or disease)
 - Limited options (i.e., there have been few innovations in the disease state, the products on the market are contraindicated for a subset or subsets of patients, or available therapy does not meet the patient's preference).

Despite ICER receiving comments from SWHR and many others on this issue, ICER continues to hold firm and leave the consideration of these important factors up to the discretion of the voting panel. Consequently, the impact of these factors is not being systematically measured. SWHR urges ICER to partner with qualified research organizations to develop, test, and pilot a methodology to integrate these factors into ICER value assessments in a transparent manner to allow for and maximize stakeholder input and collaboration.

Section 6.1 (Report Development)

SWHR Recommendation 7: 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:

- In its draft evidence report on endometriosis, ICER repeatedly acknowledged important limitations both in the available evidence and in its own analysis, which calls into question the timing of the value assessment and the validity of its conclusions.¹²
- In its final evidence report on endometriosis, the New England Comparative Effectiveness Public Advisory Council (CEPAC) “*did not deliberate or vote on the value of elagolix because the manufacturer had not yet announced the launch price, and ICER’s economic evaluation had therefore used a placeholder price.*”¹³

SWHR urges ICER to trigger the timing of its topic reviews when pertinent data (clinical trial, accurate pricing, and real-world evidence) are available.

SWHR Recommendation 8: Further extend stakeholder review times.

Value assessment organizations, including ICER, should provide ample opportunities for stakeholder engagement to ensure their input is both acknowledged and meaningfully incorporated into assessments. This includes allowing sufficient time for stakeholders to review materials and submit comments in various stages throughout the assessment process.

SWHR appreciates that ICER acknowledged this recommendation in its updated framework and proposes to extend the review time for large-class reviews by nine weeks. Extending the draft report public comment period by one week represents a modest improvement but remains inconsistent with established and customary timeframes for other stakeholder review timeframes. As discussed in SWHR Health Care Value Assessment Principle #6, federal government public comment periods typically are not less than 30 days and frequently are a minimum of 60 days.

We ask ICER to further extend stakeholder review times to be consistent with those of the federal government and other health technology assessment organizations (e.g., not shorter than 60 days).

SWHR Recommendation 9: Update assessments to account for new innovation and changes to the evidence base as needed.

SWHR agrees with ICER that “*stakeholders would benefit from a formal process to indicate whether report findings remain applicable or that new developments have occurred that could lead to different conclusions*” [lines 1424-1426].

Incorporating longer-term outcomes is important to account for the full value of a therapy or intervention, particularly as additional evidence continues to emerge post-approval. In addition, patient perceptions of value change over time as their individual circumstances and experience of illness and treatment evolve through the course of disease (i.e., shifts in prognosis, severity of illness, comorbidities, available treatment/palliative options, and life events such as pregnancy or menopause). (See SWHR Health Care Value Assessment Principle #3.)

SWHR supports ICER's proposal to implement a review process, to be completed around the one-year anniversary of a final report that will summarize in a public statement ICER's rationale for why it will or will not update the assessment. We encourage ICER to outline a well-articulated process and timeline for how it will conduct assessment updates to final reports.

SWHR Recommendation 10: Include additional information on patient perspectives.

ICER proposes to create a new chapter on patient perspectives that will follow the background chapter in its assessment reports. SWHR supports inclusion of patient-centered information in the early pages of each assessment. Such information is important for all audiences, particularly members of the voting panel, who need to have a more comprehensive understanding of the patient experience and the burden of varying illness factors. As a next step, ICER should outline its proposed process for soliciting input from stakeholders, as well as the criteria it will use to decide what patient perspective information will or will not be included in this new chapter for all future assessment reports.

Section 6.2 (Public Meetings)

SWHR Recommendation 11: Include disease experts on ICER voting councils.

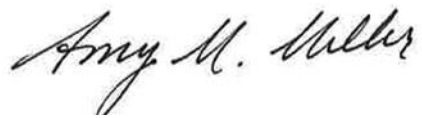
ICER's council membership by design does not necessarily include those affected by the condition under review. Seeking input from patient and clinical experts throughout the report development process does not compensate for this lack of critical representation.

Stakeholders who have direct experience and expertise with a particular illness and its burden should be appropriately represented on ICER's voting councils that make determinations about a treatment's value. As outlined in SWHR Health Care Value Assessment Principle #6, we strongly urge ICER to reconsider the design and composition of its council membership and voting councils to include representation from the following stakeholders in each of its assessments:

- Patients who are diagnosed with the disease/condition under review;
- Health care professionals who actively treat patients with the disease/condition under review; and
- Caregivers who assist patients with care needs for the disease/condition under review.

Thank you for the opportunity to provide these comments and for ICER's thoughtful consideration of our proposals. 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

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October 18, 2019

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

Submitted electronically at: publiccomments@icer-review.org

Re: Request for Public Input for 2020 Value Assessment Framework Proposed Changes

To Whom It May Concern,

UCB appreciates the opportunity to provide comments on the Institute for Clinical and Economic Review (ICER) 2020 Value Assessment Framework Proposed Changes. UCB is a global biopharmaceutical company with U.S. headquarters located in Atlanta, Georgia. Our focus is on innovating new medicines to treat chronic, severe diseases in neurology, immunology, and bone that treat nearly three million patients worldwide. We are nearly 7,500 employees globally, inspired by patients and driven by science. We have consistently demonstrated our commitment to creating more value for patients, investing approximately one quarter of total revenues into research and development for new therapies over the past several years.

UCB is committed to the continued evolution of the healthcare system toward recognizing and rewarding value through a policy environment that advances innovation, better incorporates patients in value-based care, and promotes affordable access for patients to the right medicine at the right time. In addition, UCB recognizes its obligation to our patients, the healthcare system, and society at large and is demonstrating its commitment to being part of the solution.

UCB appreciates ICER's solicitation of feedback on the critically important topic of improving its value assessment framework for prescription drugs and other health interventions. ICER's evidence reports have a significant impact on patient access to imperative and sometimes life-saving medicines and other health interventions. For this reason, it is crucial that the value assessment framework underpinning these evidence reports is deeply rooted in the most rigorous and clinically validated methodologies as possible.

As an innovator company that has been through multiple ICER reviews, UCB has real world experience in the application of ICER's value assessment framework to our medicines and the resulting impact on our patients. Based on this experience, and UCB's commitment to maximizing patient access to value-based care, we offer the following comments and questions on ICER's 2020 Value Assessment Framework Proposed Changes.

3.2 Evidence Rating Matrix: Addition of a New Summary Rating

In past ICER assessments, there has been uncertainty around specifically what differences in clinical efficacy constitute a "comparable", "small", or "substantial" net health benefit. By way of

clarification, UCB would like to know how ICER plans to establish consistency across assessments by ensuring that each evaluation applies a uniform definition of these terms.

3.2 Quantifying Additional Dimensions of Value

UCB is concerned that ICER is not proposing to separately quantify additional dimensions of value and use them to weigh the results of cost-effectiveness analyses. We encourage ICER to introduce shared decision-making components to the analysis or heighten its focus on endpoints most important to patients, in addition to considering the primary efficacy endpoints from clinical trials. UCB supports policy approaches that support informed, shared healthcare decision-making and incorporate patient perspectives and real-world evidence in value assessments. Other value frameworks have evolved to more formally include additional dimensions of value and, as a result, may be better positioned to provide a more holistic evaluation of cost-effectiveness and value. We urge ICER to recognize the value of weighing these considerations in both the clinical differentiation assessment and the base-case cost-effectiveness model. UCB also encourages ICER to be transparent about, specifically, which elements are quantifiable, and which are not. Lastly, UCB recommends that ICER continue to explore ways in which to quantify additional dimensions of value.

We also propose that ICER prioritize cost-effectiveness and cost-per-outcome analyses rather than cost per quality-adjusted life year (QALY). Particularly in the case of unexplored disease areas, QALY assessments are not always successful in capturing the holistic patient value and a more nuanced assessment is needed.

3.3. Cost-Effectiveness Threshold Ranges

Historically, “value-based” price benchmarks simply refer to the idea of additional discounting to meet proposed thresholds. However, UCB is concerned that, if frameworks do not evolve to capture all or, at least more, elements of value, the benchmarks are not reflective of a truly value-based assessment or price. We encourage ICER to consider alternative methods that take a more nuanced approach to assessing value in developing treatments and would consider the elements of value that are most important to patients. UCB is committed to supporting the healthcare system’s evolution to better account for value and allow and encourage innovation for patients.

Additionally, UCB has concerns that ICER thresholds are arbitrarily set and that, in adopting a common set of cost-effectiveness thresholds across all product assessments, ICER deviates from its stated goal of “fairly reward[ing] innovators for the value they bring to patients, and provid[ing] them ample incentive to pursue the investments and research that will lead to the innovative treatments of tomorrow”. ICER’s use of a standardized set of thresholds fails to recognize the contextual nuances inherent in the attributes of rare disease and chronic severe disease treatment options. UCB fears that this failure could limit patients’ access to lifesaving treatments and feels strongly that patients should have access to treatments that best meet their individual needs. We urge ICER to carefully consider any changes to its framework that could effectively limit patients’ access to treatments.

3.6 Alternative Economic Modeling Assumptions

ICER proposes to add a “Controversies and Uncertainties” element to the cost-effectiveness section of its reports. UCB requests clarification on how these elements are being defined, how

transparency and consistency will be achieved, and whether these “controversies and uncertainties” will be available for exploration in the model made available to external stakeholders.

UCB has concerns about ICER’s decision to conduct and conclude value assessments for treatments that have not yet, or have only just, received approval from the U.S. Food and Drug Administration (FDA). We support policy approaches that encourage innovation in the development of new transformative medicines and fear that assessments of not-quite- or newly-approved treatments may be incomplete and do not adequately capture the treatment’s elements of value. Premature assessment of new therapies makes it even more important to have transparency around alternative modelling assumptions to account for data uncertainties.

3.7 Other Changes

ICER states that it will seek information from manufacturers and payers with which to model as a scenario analysis a limited number of outcome-based payment arrangements for the intervention under review. UCB requests clarification from ICER regarding the circumstances under which outcomes-based concepts would be considered.

5. Potential Other Benefits and Contextual Considerations

ICER proposes changes to the Proposed List of Voting Questions on Potential Other Benefits/Disadvantages and Contextual Considerations. UCB requests clarification on two points:

1. How does this proposed change align with “additional dimensions of value” and their exclusion from formal cost-effectiveness evaluations? How are benefits selected and chosen for inclusion versus exclusion?
2. Can ICER clarify its statement around adding “one new potential disadvantage related to treatments”? How and when is this disadvantage identified and included?

6. Report Development and Public Meetings

Patients are at the center of everything we do at UCB. Our patient value strategy, which aims to deliver unique outcomes that help specific patients achieve their goals and the best individual experience while improving as many lives as possible, underpins our decision-making and strategic engagement. As a company, UCB is committed to incorporating the patient voice in drug discovery, development and care delivery. We continue to focus on innovation to address unmet patient needs and support policies that align with delivering meaningful value to patients. As such, UCB supports the consideration of “patient perspectives” in future cost-effectiveness analyses and requests clarification from ICER regarding how it intends to formally incorporate these perspectives.

7. Stakeholder Engagement

UCB requests more detail regarding how ICER plans to ensure that committee members have a strong understanding of ICER’s methods and assumptions in their interpretation of the results to make informed voting decisions. At previous meetings, the level of detail and time taken to review assessment

results has been integral to members' ability to make informed decisions. If the process is not outlined and followed consistently, we fear the results of the voting process could be misleading.

* * *

UCB respectfully appreciates this opportunity to comment. We welcome further discussion with ICER on improvements to the 2020 Value Assessment Framework Proposed Changes. Please contact Amanda Ledford, Associate Director of U.S. Public Policy, at Amanda.Ledford@UCB.com or 202-893-6194 with any questions or feedback on our comments.

Sincerely,



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Inspired by **patients.**
Driven by **science.**



October 15, 2019

Steven D. Pearson. MD
President
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Submitted via email: publiccomments@icer-review.org

Re: Public Input to Proposed Changes (2020 Value Framework)

Dear Dr. Pearson,

Thank you for the opportunity to submit these comments on the Updates to 2020 Value Assessment Framework Methods and Procedures developed by the Institute of Clinical and Economic Review (ICER).

ICER recognizes the inherent tension in the system between public and private payors/healthcare plans and drug manufacturers with patients and physicians requiring choice and access to the right medicines at the right time at affordable prices. The US current spends close to 18% of its GDP on healthcare¹, more than any other country yet many patients are still left with very limited access to healthcare, face high out-of-pocket costs and encounter unpredictable quality of care².

ICER developed the first draft of the value framework and received broad and detailed input from ninety-seven organizations and individuals that highlighted both strengths and some critical issues with the framework with recommendations to improve it. My comments highlight some overall key fundamental points that are still relevant to this updated framework and provide suggestions on moving forward to a more comprehensive framework for determining value in the context of decision-making for drug pricing.

Threshold for determining cost-effectiveness in the US

ICER notes that it will provide pricing benchmark results using standardized cost-effectiveness thresholds from \$50,000-\$200,000 per QALY and per evLYG – a benchmark that will be extended to ultra-rare disorders.

The determination of thresholds is obviously a critical step towards determining the cost-effectiveness of therapies as any therapy that falls below this threshold is considered cost-effective or value for money. Funding this technology at the stated price will therefore result in more health gains than what is lost through displaced therapies or activities. Those that fall above it is considered not cost effective and ICER determines the discounts necessary to make it fall within its stated threshold range.

Even with ICER extending its range to \$200,000, it should be noted that these threshold ranges are not derived from empirical and scientific studies. Hence the validity of these thresholds especially as it applies to the US healthcare system may not be strong. If CEA thresholds are going to be used to determine value-for-money, it has to be set appropriately taking into account critically the perspective of the decision-maker in particular. This decision-maker (either Medicare or a commercial health plan) is the one that holds the budget and pays for the healthcare intervention and has a defined patient population that is under its coverage. If this threshold is appropriately determined, it will serve to improve both the effectiveness and efficiency of the health system under consideration by the decision-maker. However, if set inappropriately, it may not lead to decisions that reflect the true value of the therapies, lead to optimal patient outcomes or bring about increased affordability.

Hence the importance of perspective in any cost-effectiveness analysis. Even in healthcare systems that use cost-effectiveness analysis for decision-making (and these methods are generally practiced and polished in countries with single-payor, publicly-funded healthcare systems), there is recognition that this thresholds are not empirically determined. Hence there is unwillingness to depend solely on this measure, ongoing confusion on interpreting cost-effectiveness and reluctance by policy-makers on using this measure to determine price. For this reason, launch or submitted prices of new drugs

that are deemed not cost-effective are left to complex rounds of negotiations between the individual payor and manufacturer to determine the final price for reimbursement. These prices are often confidential and can vary amongst payors (private health plans vs public-funded health plans) and jurisdictions even within the same country. That negotiated price represents the willingness-to-pay price by the payor that is deemed to represent the value of the drug or therapy to their health plan.

The threshold range suggested by ICER does not seem to be theoretically or empirically supported and it is unclear to what precise perspective it represents. If ICER can determine a threshold for specific payors (e.g. a threshold for a specific commercial healthcare plan or a threshold specific to Medicare where either groups have distinct budget and distinct patient population), it will be more useful and valid for identifying cost-effectiveness of a new therapy for that particular payor. This is an issue not just peculiar to the US healthcare system but for all HTA healthcare systems that actively use thresholds to determine cost-effectiveness.

Further, does this threshold reflect the shadow price or does it reflect willingness to pay³. If the latter and if this can be determined in robust empirical ways grounded by economic theory, the adoption of such thresholds can contribute toward improving the effectiveness, quality and efficiency of the US healthcare system. If the threshold reflects willingness to pay, should not past decisions on funding by payors reflect the baseline threshold level so all future therapies are measured against this baseline?

Use of Cost-effectiveness as tool to determine value based price

Maximizing health whether measured by QALYs or evLGYs is a useful criteria but not the sole criteria in determining value-based price. It can still remain a useful benchmark for deliberations. Pricing is often based on many factors including the absence of any other therapies (unmet clinical need), the severity of the illness, epidemiology, sunk costs, return of investments, reward for risk-taking, future investments for greater innovative products, patient values, societal values and many

other policy and business factors. As ICER recognizes in the updated value framework, these other factors including patient perspectives, need to be taken into account in determining a value-based price but these other factors cannot be quantified and therefore incorporated to arrive at a price. What is therefore needed is a decision-making framework that view cost-effectiveness as just one element of determining the value of a new drug or therapy.

The use of cost-effectiveness for any decision-making either setting a price or determining negative or positive recommendations has to distinguish questions relating to what is a fact verses what is value. Fact involves determining the opportunity cost of adopting the new therapy. Value refers to the importance placed by the public (or payors) on the new therapy and those therapies/drugs that need to be forgone. The determination of a robust scientifically derived threshold can provide the foundation for the fact. Since this is missing, the reliance on thresholds may not be appropriate for the US context.

Value-based forms of pricing may work for commodities but in the context of therapies where lives and quality of individual lives are at stake, the determination of price using cost-effectiveness analysis as the sole basis can be problematic⁴. Even if a therapy is considered cost-effective, it still may not be affordable by the payor based on total eligible patient population hence there has been methods used in other jurisdictions such as competitive tendering, price-volume agreements, performance-based agreements, expenditure caps and bulk purchasing to determine pricing for affordability.

ICER also notes that its choice of using threshold aligns with the recommendation by WHO of using three time the GDP/capita, However, WHO has backed out of setting these fixed benchmarks as it was originally formulated to get countries to fund basic interventions for public health mostly in developing countries. The exact transfer of this threshold to more advanced economies may not be applicable⁵. Further work from Phelps using a new conceptual framework can shed more light on this threshold question.

Value-based pricing was attempted in UK and in all effects put on hold though it did introduce risk sharing agreements with manufacturers with evidence development arrangements and enabled additional dimensions to be considered (such as innovation and end of life adjustment) to cost-effectiveness. The point is these negotiated schemes are necessary to extract dynamic and static efficiencies from the use of drugs. There is a need to have a deliberative decision-making process to arrive at pricing decisions that enables affordability by payors and disincentive price gouging by manufacturers for drugs that do not show sufficient magnitude in clinical and safety benefits compared to existing therapies. Negotiated agreements also enables flexibility in pricing allowing price discounts when the same drug shows minimal added benefit for a particular new indication (i.e. multi-indication pricing).

Non-CEA threshold HTA systems

Due to these issues around interpretation and determination of thresholds, the German system (as well as France, Switzerland and others) do not evaluate drugs based on cost-effectiveness but instead focus on the determination of added patient benefit followed by several rounds of negotiation or reference pricing.

In the German system, the magnitude of clinical benefit (6 categories: major, considerable, minor, non-quantifiable, none, less) is defined and quantified. In cases where no major benefit is found with respect to current therapies already available, then reference pricing is triggered where the drug price is reimbursed at the price set by the lowest priced competitor. This process would tend to discourage the development and commercialization of 'me too' drugs for the disease indication and steer companies towards developing innovative products that bring substantial clinical benefit to patients and improve safety that can lead to significant downstream cost savings to the payor. Even if a 'me too' drug is developed, manufacturers will be aware in advanced that they need to price it at rates similar to existing competitors and can strive instead of capturing market share.

As such, instead of providing a crosswalk between ICER's evidence rating with those of the German system or even the French ASMR system, it might be more beneficial to contrast and highlight the difference for each drug being reviewed where ICER's net benefit rating might be different from these other ratings.

Lastly, ICER's review of drugs would need to match the actual indication approved by the FDA as this is the only indication that will be available to patients. In cases where the FDA provides a breakthrough designation, ICER could automatically place this product in the top tier of its added net benefit ranking.

Towards a Deliberative Decision-Making Framework

If ICER continues to incorporate cost-effectiveness, this may need to be regarded as just one dimension in a multi-dimension decision-making framework for pricing recommendation. Most of these other important dimensions cannot be quantified and hence cannot be incorporated within the cost-effectiveness analysis to arrive at a value based price. As such, ICER may want to develop a framework that can provide guidance to payors on how much they are willing to pay for new drugs/new indications based on direct negotiations with the manufacturers that may include performance-based arrangements and indication-based pricing.

Deliberate decision-making frameworks have been developed by many HTA agencies and can have the following six value dimensions⁶: A deliberate process enables the integration of evidence from different sources to arrive at a pricing guidance. These include scientific context-free evidence (relates to the clinical benefit), scientific context-sensitive evidence set in realistic scenarios and colloquial evidence (e.g. patient impacts) to fill in any evidence gaps⁷.

ICER may want to consider its evolving role as an entity providing guidance by developing comprehensive analysis using such a framework that can be ultimately be consumed by industry and health plans to arrive at a negotiated value-based price.

A decision-making framework of this nature may incorporate the following six dimensions as part of setting a funding price:

- **Clinical Benefit:** Quantifies net health benefit taking into account both incremental efficacy (as measured by clinical endpoints relating to patient outcomes relevant to the therapeutic area) and harms/safety (frequency and severity of adverse effects) of the therapy with respect to current treatments, systematic review and clinician inputs. ICER may also want to consider exemptions to its evaluations such as non-drug pioneering therapies such as CAR-T and drugs for ultra-rare hereditary diseases.

Once the clinical benefit has been determined, these other elements can subsequently be considered.

- **Cost-Effectiveness:** Measures net efficiency and determines this in relation to current treatments based on the current or launch price and compares to pre-determined ICER thresholds.
- **Unmet Clinical Need and Severity of Illness:** Determines existing choices available that can bring about the similar outcomes. (A drug that is considered cost-effective in a field of many similar drugs may therefore still be subject to pricing that is similar or lower to existing branded or generic products). Similarly a drug with no other comparators (e.g. for rare hereditary diseases) should be able to gain a premium even if it's considered not cost-effective).

- **Affordability:** The epidemiology of the disease (incidence/prevalence) to be considered in relation to the budget impact to the payor. This should include any companion diagnostic tests costs. Normally, this is left to the payor or manufacturer to be determined as this involves business assumptions regarding take-up rate and market share growth. Most budget impact analysis are currently already done by the manufacturer with both commercial payor and Medicare perspectives and incorporated in AMCP dossiers for the drugs.
- **Patient Perspective:** Enables incorporation of patient preferences and values and out-of-pocket costs to patients.
- **Negotiated Arrangements:** Considered where complex deals between health plans and manufacturers may involve differential pricing that are indication specific, bulk purchasing discounts, outcomes-based agreements, risk-sharing, performance-based agreements, flexible pricing, response based agreements, expenditure caps and other negotiated deals. ICER's guidance can encourage such arrangements to be made between payors and manufacturers taking into account implementation issues.

Any price determined between payors and manufacturers may need to consider these factors as cost-effectiveness alone cannot incorporate all these dimensions and therefore should only be considered as one of the several factors to be incorporated in the recommendation of any value-based price.

Going Beyond Drugs and Therapies

Nearly 30% of healthcare spending in the US can be consider waste and this was estimated to be up to \$935 billion in annual costs. Recent analysis⁹ has identified six main waste domains that include failure of care delivery, failure of care coordination, overtreatment or low-value care, pricing failure, fraud and abuse and administrative complexity. ICER attempts to address pricing failure which was estimated to range from \$81.4 billion to \$93.3 billion savings if this can be addressed. Other areas

identified include looking at payor models and pricing transparency for lab and office visits. There still remains other areas of eliminating healthcare cost that ICER may want to analyze especially overtreatment/low-value care, use of branded vs generics, use of prior authorizations and optimizing medication use.

Other points

ICER is in a position to provide pricing guidance based on a comprehensive deliberative framework. Ultimately, the listing price is a negotiated price between the Medicare and commercial payors (who holds the budget and accountable to their members) and manufacturers where decisions are made to maximize profit.

Price premiums can be used to encourage development of drugs in areas where no other therapies exist. As noted by NORD, there are 7000 rare diseases and 90% have no FDA-approved therapies. At the same time, many trials currently having multiple high-priced biologics added to one another. These can contribute to rising drug costs and it is not clear how these additional therapies (e.g. double or triple immunotherapies) work. There is need to understand the mechanism of action as previous studies have shown that this could be due to specific drugs in the combination therapy having effects on different subgroups within the same trial population rather than due to any synergistic effect of multiple drugs on the same patient.

ICER's analysis can encourage payors to engage in negotiations with manufacturers to arrive at a value-based price with possibilities of using any savings to offset out-of-pocket costs for its members.

Conclusion

ICER has made major strides to take on this challenge of managing rising healthcare costs that may not reflect either improved patient access or patient outcomes and has brought current drug pricing to the forefront of evaluation and discussion. In the short-term, ICER might consider using CEA as part of a larger deliberative decision-making framework to determine value. This can serve as critical

input to payors who can leverage this framework to assist in negotiations with manufacturers. ICER might also want to consider the use of value of information (VoI) analysis¹⁰, and present results using probabilistic sensitivity analysis and cost-effectiveness acceptability curves (CEAC) as WTP can differ by payors/health plans.

In the longer term, ICER might develop empirical based thresholds for different payors (public vs private) or use entirely different conceptual framework to quantify cost-effectiveness.

I look forward to be able to engage further with ICER as it continues to develop and enhance this value framework.

Sincerely,

Mayvis Rebeira

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Center Research Fellow

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