

Darron Segall, MHS
Manager, Global Market Access
Abbott Diabetes Care

To Whom It May Concern,

I am writing on behalf of Abbott, a global healthcare leader, to express our support for the proposed changes to the Institute of Clinical & Economic Research's (ICER's) Value Framework for 2023. We believe these updates can enhance the evaluation of clinical and economic value in healthcare interventions.

Diverse Patient Engagement, Accessibility, Inclusivity

- The proposed enhancements to the patient engagement program will improve our collective understanding of the patient's lived experience and perspective
- The inclusion of patient and caregiver testimonials and small-group discussions will amplify diverse patient community voices
- The focus on clinical trial diversity and subpopulation analyses aligns with FDA guidance and helps to ensure more equitable access to healthcare and aligns

Real World Evidence (RWE), Pricing, Cost Effectiveness

- Abbott supports ICER's efforts to seek opportunities to use RWE within assessments. We believe it will be particularly useful for those technologies showing utility that outpaces the data, e.g., randomized control trials; additionally, it is supportive of the FDA's position on using RWE for post market safety analysis and to make regulatory decisions
- The introduction of dynamic pricing scenarios can provide a more accurate assessment of cost-effectiveness as well as a better reflection of the quality and reliability of the intervention being assessed
- ICER's consideration of economic models and holistic impacts aligns with a more comprehensive evaluation approach
- ICER's commitment to using both the Quality Adjusted Life Year (QALY) measure at the \$100k threshold, and Equal Value of Life Years Gained (evLYG) measure at the \$150k threshold contribute to a more comprehensive evaluation of interventions as well as allowing flexibility for policymakers

In conclusion, Abbott supports ICER for the proposed changes. The proposed changes will further promote transparency, inclusivity, diversity, and a commitment to continually improve the determination and evaluation of value. We believe that these modifications will foster a more collaborative and transparent environment increasingly driven by inclusion of RWE which, collectively, will facilitate more informed and fair value assessments.

Thank you for considering our perspective. Should you require further information, please do not hesitate to contact us.

Sincerely,

Darron Segall, MHS
Manager, Global Market Access
Abbott Diabetes Care

June 22nd, 2023

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

Sent Electronically to publiccomments@icer.org

RE: Public Comments 2023 ICER Value Assessment Framework (VAF) and Processes for Conducting Value Assessments - Proposed Changes

Dear Dr. Pearson:

AiArthritis (International Foundation for **Autoimmune & Autoinflammatory** Arthritis) is dedicated to patient-led advancements in education, advocacy, and research for those impacted by autoimmune and autoinflammatory arthritis (**AiArthritis**) diseases through peer-led guidance, collaboration, and resources that are driven by patient-identified issues and patient-infused solutions. As we are led by patients we understand the importance of ensuring better health outcomes and lower costs for our peers, which includes those living with chronic diseases like Psoriatic Arthritis, Rheumatoid Arthritis, Lupus, Spondyloarthritis, and over a dozen other **AiArthritis** Diseases.

AiArthritis shares ICER's goals to improve fair access to treatments and lowering costs for the healthcare system. While there are several areas we could address, given our expertise in clinical trial diversity, subgroups, and patient input in healthcare issues, our feedback and recommendations will focus largely on these areas. **We appreciate this opportunity, particularly as these comments are formulated from the perspectives of those who will be impacted most by your assessments.** *Community comments are captured in detail in a project report.*¹

While **AiArthritis** and ICER share common goals to provide fair access, there are some fundamental differences to note. ICER reviews therapies at a "population" level versus at a **disease subgroup** ("**subgroup**") level. For **AiArthritis** diseases, subgroups may be based on several factors, including disease severity (mild, moderate, severe), access to early intervention, existing damage, comorbidities (present in over 70% of patients), and varied disease classifications (i.e. early Rheumatoid Arthritis, Difficult to Treat/D2T).²

Again, we thank ICER for this opportunity to include patients 'at the table', for considering our comments, and for recognizing the need to include more of us in the Health Technology Assessment (HTA) process.

Our collective **AiArthritis** and peer input comments and recommendations are as follows:

1. **The Population Perspective and Intended Uses of the ICER Value Framework.** We would like to take this opportunity to point out that there is a broad spectrum between “population” level and attempting to create a value framework intended to support decision making at an individual, shared decision making level. Even in this proposed update, ICER mentions more considerations and inclusion of subpopulations and subgroups. Additionally, considering research into subgroups, largely Precision Medicine (PM), is already utilized in the clinical setting in cancer and is soon to follow in other disease groups like **AiArthritis**. PM does not always mean “individualized therapy” - or “n of 1” - but often means n of 1,000’s (*subgroups*). Soon value assessments will require the inclusion of this data and, in turn, the inclusion of subgroups.

We understand that “*population-level decisions and policies have always been made by life science companies, insurers, and clinical organizations looking at evidence in the same general way,*” which ultimately leads to later access issues for those who do not fit into the mold of average patients. ICER’s attempt to bridge this gap between individuals and population level involves *including what is or is not known about the variation in response to different treatments among patients with different personal and clinical characteristics and consideration of elements of value that are important to individual patients but that fall outside traditional clinical measures.* **But given we know individual level data falls on deaf ears, and realistic patient populations involve a series of subgroups, what is ICER planning to do to include the 1,000’s in between population level and n of 1? We challenge ICER to consider this question as they evolve their methodology and process in the future.**

2. **Clinical Trial Diversity.** We recognize ICER’s efforts to consider clinical trial diversity in future assessments, as without the right participants the data produced may not accurately translate to real world adaptation. **AiArthritis** expressed a similar concern in our 2015 Ethics of Step Therapy Investigation.³ We stated that when clinical trial participants represent a broad general population, and are not truly representative of the subgroups that exist within the diagnosis, insurance companies should not be allowed to use that data to justify treatment recommendations for those underrepresented in the data cited. Interestingly, while our focus in this study was disease subgroups, the same conclusion could support rationale for increased demographic representation in trials. ***It also highlights the need to evolve VAF’s away from population level models in conditions where heterogeneity and clear subgroups have emerged, and move towards methodology that promotes equity, inclusion, and value relevant to all groups who share a diagnosis.***

We acknowledge there are challenges, particularly in regards to diversity in data, and we appreciate ICER’s dedication to incorporating health equity into their VAF. However, additions of somewhat generic tools like the HIDI and Diversity Ratings do little more than point out something we already know - the clinical trials over the last decade lack diversity. We believe it is vital to assess reliable

disease-specific prevalence estimates along with these ratings, but we are concerned when no reliable estimates are available that the default consideration is simple comparison to population estimates.

In the absence of high quality evidence, and if we do not know how the clinical outcomes and cost could affect a subpopulation or subgroup, generalizing the group seems opposite of ‘equity’. Therefore, we **feel that when data is limited and the proper ratio of subpopulation to known disease effect is not accurately represented, then it is ICER’s responsibility to establish a clear and transparent process for determining discontinuation of the assessment.**

- 3. Subpopulation Analysis.** We appreciate that ICER is incorporating more consideration to heterogeneity and disease burden, including the addition of the ICEMAN tool to evaluate the credibility of subgroup findings. **While we are pleased to learn this tool measures variables such as comorbidity, age, and disease severity, we are unclear how ICER plans to effectively utilize this in conjunction with methods like the QALY and evLYG.**

Additionally, there are specific differences between the term ‘subpopulation’ and ‘subgroup’, yet in this section of the report ICER often uses them interchangeably. ‘*Subpopulation*’ refers to demographics (race, ethnicity, age, etc.) and ‘*subgroup*’ refers to disease severity or gradations of disease and associated groups with one diagnosis. There will also be many situations when research participants overlap into the various groups. Failure to differentiate the two and their intended incorporation of data from them alludes to perceptions that perhaps only ‘subpopulations’ will only truly be considered. **We recommend that ICER clearly defines ‘subpopulation’ versus ‘subgroup’ and outlines how each will be considered within the context of “Heterogeneity and Subgroups” and when utilizing the ICEMAN assessment tool.**

- 4. Patient Engagement Program.** AiArthritis was founded on the belief that patient voices hold the key to identifying issues that those void of lived experience cannot see. Therefore, true innovation will only happen when the patient voice is present ‘at the table’. **We applaud ICER for your efforts to activate more patients into the HTA experience.**

However, we have identified potential issues with ICER’s plans to invite more patients - specifically those not affiliated with patient groups - to the HTA process:

- **Current patient engagement opportunities posed by ICER are *still* too high level and, realistically, patients who are not associated with patient groups would be largely unlikely to participate.** ICER states they have listened and heard from patient input that communications remain too high level, technical, and out of reach for many patients - and “ICER has been working with patient leaders” to eradicate this issue. However, [this ICER call for comments is the perfect example](#) of why efforts are still lacking. On the webpage for this ask, while there is a request for all stakeholders to weigh in, the bulleted requirements and the report itself are both

too intimidating and limiting (i.e. “5 pages maximum (excluding references and an appendix that may only contain data tables and figures from published evidence or gray literature, but not additional commentary.”). If ICER truly wants a variety of patients, particularly those not affiliated with patient groups to start weighing in, this method of submission needs to be altered.

- **While we appreciate ICER’s efforts to improve their qualitative understanding of the patient lived experience through the Share Your Story Form, it is unclear how these testimonies will influence any part of the assessment findings** (since it is not intended to be a validated tool and given ICER historically does not include non-validated data, individual-level value needs into their decision making process).
- **To bring novice patients into the HTA process, there will be a need for easy-to-understand, unbiased education materials. Any new materials led by ICER should be co-created with patients/patient groups and existing materials reviewed, edited, and approved by patient representatives who have varied experience with the HTA process.** *We also encourage ICER to consider referencing and recommending existing educational materials groups like the National Health Council’s (NHC) Virtual Classroom and AiArthritis’ Knowledge = Empowerment, patient-led classroom, learning materials, and elevated experiences, both which cover Value Assessments.*^{4 5}

ICER Patient Council. As I am one of the six patients serving on the new Council, I would like to take this opportunity to publicly state that I appreciate the dedication ICER leadership has taken over the last year to put this into action. I also feel it is worth noting that I expressed at our initial meeting that given my strong stance on PM, subgroup analysis, and “there’s no such thing as an average patient,” I may not be the best fit for this Council. To my surprise, I was assured it is exactly why I am the right fit. We had both enlightening conversations and fiery disagreements, but in the end we pulled together something that I believe will be a positive step towards involving more patients in the HTA process.

As a patient-led organization focused on improving the lives of those impacted by AiArthritis diseases, we urge ICER to consider these recommendations. Together we can achieve the crucial goal of ensuring better outcomes and reducing costs for patients. Thank you again for this opportunity and for considering what patients feel is most important.

Sincerely,



Tiffany Westrich-Robertson

Chief Executive Officer

Person living with Axial Spondylitis

- With contributions from the greater patient community

References:

1. AiArthritis Knowledge = Empowerment Project “Elevated Experience” Opportunity: Help AiArthritis Submit Public Comments - ICER Value Assessment Framework (VAF) and Processes for Conducting Value Assessments <https://bit.ly/ICERComments63023>
2. Nagy G, Roodenrijs NM, Welsing PM, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. *Annals of the Rheumatic Diseases* 2021;80:31-35.
3. Westrich-Robertson, T., et al. Ethics of Step Therapy Investigation, white paper 2015. <https://www.aiarthritis.org/ethics>
4. <https://nationalhealthcouncil.org/education/value-classroom/>
5. <https://www.aiarthritis.org/knowledge-empowerment>



June 30, 2023

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
14 Beacon Street, Suite 800, Boston, MA 02108

Re: 2023 Value Assessment Framework Proposed Changes:

Dear Dr. Pearson:

The Alliance for Regenerative Medicine (ARM) is pleased to provide comments in response to the Institute for Clinical and Economic Review (ICER) June 5, 2023, request for input on the 2023 Value Assessment Framework (VAF) proposed changes.

ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis. We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 475 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

As of year-end 2022, there were 1,457 engineered cell therapy and genetic medicine developers worldwide sponsoring 1,070 clinical trials (out of 2,200 clinical trials globally, which are also sponsored by academic and government institutions) across dozens of indications, including rare monogenetic diseases, oncology, cardiovascular, central nervous system, musculoskeletal, metabolic disorders, ophthalmological disorders, autoimmune diseases, and more.¹

The health technology assessment (HTA) evaluation issues presented in this iteration of the ICER VAF proposed changes contain three areas where ARM applauds ICER: (1) the patient engagement program, (2) clinical trial diversity considerations, and (3) real-world evidence priorities.

Patient Engagement Program

ARM commends ICER's commitment to building on the 2020 VAF to enhance the patient voice and compensate patient representatives for their time and contributions, and ARM strongly urges similar enhancement in valuing of the patient life and perspective across all components of the VAF.

¹ <https://www.alliancerm.org>



Clinical Trial Diversity

ARM applauds ICER's efforts on this topic and stands with the organization to focus on continued diversification of clinical trial demographics. ARM is committed to supporting all patients having access to life saving care. Inclusion of a diverse clinical trial population is key to removing biases and demonstrating benefits across demographics. With that said, in some cases, such as some rare diseases, factors that drive a diverse trial population may not be well characterized at the time of scoring. In those cases, scoring is not possible; and in all cases of scoring, more transparency related to the detailed methodology is warranted.

Use of Real-World Evidence

ARM is fully supportive of using real world evidence to evaluate gene and cell therapies and finding innovative solutions for incorporating real-world evidence into trial planning, trial endpoints, and outcomes research.

With the emergence and expansion 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.”² 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.”³ ARM agrees, and further suggests that while expectations are that the patient outcomes will be durable over the long-term, it is important that payment may be incurred and settled at the time of treatment in many cases.

In addition to these points of appreciation, however, ARM has critical concerns with certain proposed changes as detailed below. From a general approach standpoint, the comment period provided for these VAF revisions is inadequate. ARM recommends ICER allow at least 60 days for stakeholders to provide meaningful input on future proposals. Additionally, the proposed changes are more restrictive than prior VAF revisions, each of which creates significant barriers to ICER obtaining meaningful input.

Limitations of Traditional HTA frameworks

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 totality of 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 the U.S. and Europe are not flexible enough to appropriately evaluate potential cures and do not capture

² [ICER Launches International Collaborative to Develop New Methods to Guide Value-Based Pricing of Potential Cures - ICER](#)

³ [ICER Seeks Public Comment on Proposed Methods Adaptations for Assessments of Potential Cures and Other Transformative Therapies - ICER](#)

the full product value due to issues including: the short-term timeframe 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 framework.⁴

ARM has also noted in prior statements that 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.

ICER states that “the purpose of the value assessment framework is to form the backbone of rigorous, transparent evidence reports that, within the broader mechanism of stakeholder and public engagement, will help the United States evolve towards a health care system that provides fair pricing, fair access, and a sustainable platform for future innovation”. In the spirit of fulfilling this mission, ARM suggests that ICER should endeavor to be as broad, inclusive, and fair as possible about its methods and assumptions, not less inclusive or less fair as could be suggested by current approaches in the 2023 ICER VAF proposed changes. One example of a planned approach in the 2023 VAF in direct opposition to inclusivity and fairness is the suggested use of a lower set of QALY thresholds but not higher thresholds where appropriate.⁵ 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.⁶

⁴ See October 18, 2019 ARM letter to ICER regarding the proposed update to the ICER Value Assessment Framework. <https://acrobat.adobe.com/link/review?uri=urn:aaid:scds:US:64f9e9cb-aad2-34bd-91f2-9d8d74cb8815>.

⁵ Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer.org/wp-content/uploads/2023/06/Proposed-VAF-Changes-For-Public-Comment_For-Publication_06052023.pdf. Published 2023.

⁶ Research by Neumann and Kim find that US CEAs increasingly cite a range of \$100,000-\$150,000/QALY and thresholds for oncologic CEAs are higher than non-oncologic CEAs, suggesting that “diseases associated with greater mortality and morbidity warrant higher thresholds.” Neumann PJ, Kim DD (2023). Cost-effectiveness Thresholds Used by Study Authors, 1990-2021. JAMA, 329(15):1312-1314. Available at: <https://jamanetwork.com/journals/jama/fullarticle/2803816>;

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.

Health Benefit Price Benchmarks (HBPB)

Further concerns ARM maintains with the 2023 VAF proposed adaptations are largely focused on the Health Benefit Price Benchmarks (HBPB). Under this section, for proposed change 1.b., ICER states that *for the [HBPB] of high-impact single or short-term therapies (SSTs), or of other treatments with relevant and substantial potential cost offsets, ICER will continue to consider the results of two scenario analyses:*

- i. *A 50/50 shared savings model in which 50% of the lifetime health system cost offsets from a new treatment are “assigned” to the health system instead of being assigned entirely to the new treatment; and*
- ii. *A cost-offset cap model in which the health system cost offsets generated by a new treatment are capped at \$150,000 per year but are otherwise assigned entirely to the new treatment.*

ARM has several concerns with the direction of the discussion in this section. The first of these concerns is regarding how cell and gene therapy benefits are directly related to the treatment. These are potentially curative therapies that contain the capability to stop disease and restore partial or full quality of life. To minimize the contribution of the therapy, such as in the first scenario of a 50/50 split, and only assign half of the lifetime cost offset to the treatment will unfairly erode the actual value of the treatment. This will discourage further research into the cell and gene sector as it limits the cost offset value assigned to these important new therapies, thus unnecessarily creating inequality between cell and gene therapy and traditional medicine.

Another concern for ARM is that capping cost offsets generated at \$150k per year is not feasible. As stated above, a gene or cell therapy has the potential to offer substantial cost offsets to the healthcare system. While the idea of setting a cap for healthcare system benefits is not entirely unreasonable, the cap for such benefits should be lower, thus allowing for more of the cost offset to directly be tied to the treatment. For example, if a cell or gene therapy can prevent a disease that has an ongoing cost of management of \$200k per year, it is the treatment intervention that will be responsible for those cost offsets. Additional cost offsets realized by the healthcare system may exist, but the heterogeneity of diseases ARM members invest in preventing, curing, and treating requires that there be a low capitation assigned so that much of the benefit (i.e., the large majority) can be aptly attributed to the treatment.

In the discussion section following proposal 1.b., ICER mentions that *although studies have explored the willingness-to-pay thresholds for cost effectiveness from both the health care system and societal perspectives, limited research has been conducted to estimate the opportunity-cost threshold from the societal perspective. If research expanded upon the Vanness et al. study to include broader societal domains within an opportunity cost paradigm, it would show a*

In 2021, the Congressional Budget Office (CBO) used a value of statistical life year of \$388,000/life year and willingness-to-pay values of \$507,000/QALY, including sensitivity cases used values that were 50 percent higher and 50 percent lower. Adams, C. Herrstadt, E. (2021). CBO’s Model of Drug Pricing Negotiations Under the Elijah E. Cummings Lower Drug Cost Now Act. Congressional Budget Office. Available at: <https://www.cbo.gov/system/files/2021-02/56905-Drug-Price-Negotiations.pdf>.

decreasing threshold from the original estimate of \$104,000 per QALY with each added broader societal element.⁷

The primary assumption of the Vanness study referenced in this section is that decision makers wish to get the most population health for what is already spent on health care. ARM takes issue with such an analytical approach when considering Single or Short-Term Transformative Therapies (SSTs) for the following reasons:

- There have been numerous published studies providing estimates of the wasteful spending on many current chronic therapies and ARM suggests that this wasteful spending for chronic therapies can and should be replaced versus expanded upon.
- A paper by Garrison and colleagues (2019) makes a compelling argument for higher cost-effectiveness thresholds for emerging gene therapies.⁸ One contention is that prior research efforts to estimate the value of a statistical life provided results ranging from \$4.6M to \$15.0M, with a mean of \$9.6M that implied a roughly \$315k threshold per life-year gained. The Garrison paper also indicates that evaluations of highly specialized technologies by NICE in the UK have implied thresholds reaching \$309k per QALY.
- In addition, for many one-time, potentially curative gene therapies in development, there are competitor chronic therapies being developed for similar diseases. Reimbursing one-time gene therapies can help avoid the addition of these future costs to the system, a scenario not currently addressed in ICER models.

While ARM strongly supports ICER considering the societal perspective as a co-equal case, ICER should always leverage its public reports and public comments to discuss the HBPB in the context of the co-equal case societal perspective rather than focusing public comments on proposed pricing based solely on payer perspective. This approach should also include patient and family quality of life and the potential for increased productivity into the HPBP framework.

ARM appreciates the opportunity to provide our perspective on these important issues. Please feel free to contact Brett Logan at blogan@alliancerm.org with questions.

Sincerely,



Erica Cischke, MPH
Vice President, U.S. Government Affairs
Alliance for Regenerative Medicine

⁷ Vanness DJ, Lomas J, Ahn H. A health opportunity cost threshold for cost-effectiveness analysis in the United States. *Annals of internal medicine*. 2021;174(1):25-32. [A Health Opportunity Cost Threshold for Cost-Effectiveness Analysis in the United States - PubMed \(nih.gov\)](#).

⁸ Garrison LP, Jackson T, Paul D, Kenston M. Value-based pricing for emerging gene therapies: the economic case for a higher cost-effectiveness threshold. *J Manag Care Spec Pharm* 2019;25(7):793-799. [Value-Based Pricing for Emerging Gene Therapies: The Economic Case for a Higher Cost-Effectiveness Threshold \(jmcp.org\)](#).

June 30, 2023

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review (ICER)
14 Beacon Street
Boston, MA 02108

Comments submitted via: publiccomments@icer.org

RE: ICER proposed updates to the 2023 Value Assessment Framework (VAF)

Dear Dr. Pearson,

Thank you for the opportunity to comment on ICER's proposed change to the 2023 Value Assessment Framework (VAF). AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialization of prescription medicines, primarily for the treatment of diseases in the following therapy areas: Oncology; BioPharmaceuticals (including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology); Vaccines and Immune Therapies; and Rare Disease. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide.

Our comments focus on several areas of the proposed changes and are delineated below by relevant section of the VAF proposed changes document.

Section 2.1 Clinical Trial Diversity

We applaud ICER for considering the timely issue of clinical trial diversity in the VAF. However, we question the approach offered in the VAF proposed changes document. First, it is unclear on how clinical trial diversity will inform an ICER assessment. Is there a minimum threshold of diversity and how would that threshold affect the methodology? How will the considerations of diverse patient groups be incorporated into assessment of their needs, disease burden on the patient and caregiver, and wider societal impact? Second, we offer that diversity will differ depending on the study population and specific disease. The VAF limits diversity to race, ethnicity, and socioeconomic factors. However, for some diseases, other factors may be prognostic or predictive of treatment effect, such as genetics when considering rare disease or cancer. It is important that diversity factors that impact the underlying disease are considered as well. Third, we offer the utility of information on diversity to inform disparities within the health system, especially when those disparities may be impacted by a particular treatment. For example, advanced therapy medicinal products (ATMPs) may require only one treatment which may eliminate the need for repeat treatments and provide relief to persons for whom socioeconomic factors limit their ability to regularly access health facilities.

Next, we offer that scoring, as proposed in the changes to the VAF, is problematic. The clinical trial diversity score could be misleading to patients and providers, as it does not address the clinical benefit of a therapy. Further, we are concerned about qualitative descriptions with

arbitrary cut-offs; ICER should consider a number-only rating to avoid creating any potential confusion regarding the safety and/or efficacy of FDA approved products. Additionally, we urge ICER to provide substantial transparency in how it determines a clinical trial diversity rating; including an opportunity for trial sponsors to respond. Further, due to the low prevalence and other logistic challenges, clinical trials for rare disease treatments often enroll a small number of patients. Achieving a diverse and/or representative sample is naturally more difficult when clinical trial populations are small, and the clinical trial diversity score should account for this to avoid undervaluing treatments for rare diseases.

Finally, ICER should not limit diversity data to only US trial participants. Segmenting data to create US-specific data sets may create skewed results, is inconsistent with maintaining the integrity of clinical trial data, and may lead to multiplicity issues and lower sample sizes. At a minimum, ICER must also include nuance between trials that are “representative of the racial and ethnic diversity of the US population” and global/multi-country trials that are representative of ethnic/racial make-up of certain diseases or conditions.

2.2 Subpopulation Analysis

It is unclear as to how ICER would approach subpopulation analyses; manufacturers would have to be given a notice prior to initiating studies to ensure that these populations would be investigated. Furthermore, the impact of trial diversity may be unknown at the clinical trial stage, including predictive treatment effects, particularly with novel biomarkers and mechanism of actions; in these cases our knowledge evolves as the science evolves. In addition, this application to adaptive trial design and pre-planned analyses (in a specific order depending on the result before) may create incorrect or inappropriate conclusions as data are extrapolated to subpopulations or other data segmentation for which those data were not designed, including issues of multiplicity and underpowering. Finally, we support patient and provider engagement and perspective, but believe any such inclusions would require robust volume and representative number of engagers to be meaningful.

Regarding ICER’s proposal to consider race, sex, and age as presumptive subpopulations for every review, we urge ICER to consult manufacturers as part of this process and allowed them submit appropriate evidence. Manufacturers are experts and have additional information about the medicines they develop and the diseases under consideration.

We caution against ICER’s proposal to issue separate evidence ratings for an intervention. Again, these ratings appear qualitative in nature with arbitrary cut-offs. Relative ratings or working to cross-compare evidence to support “substantial differences” may not be appropriate or consistent with standards for data and trial designs.

3.1 Perspective in Economic Models

We support ICER’s proposal to broaden the basis of value and consider the societal perspective. This is a positive step forward, but there are open questions, such as how “patient consumption costs during periods of life extension” will be defined, and assumptions such as that “carer time spent is proportional to 75% of patient formal labor time” which merit further consideration and stakeholder input. We recognize there are challenges between valuing leisure time and work productivity, and there is more that needs to be done to explore that balance and appropriate

valuation. Valuing labor time higher than leisure time may introduce a bias that values time gained by patients of working age over time gained by the young and the elderly. However, working productivity is a valuable metric on societal benefit of a medicine.

3.2 Dynamic Pricing Scenario

We have concerns with the proposed dynamic pricing scenario and urge ICER to be clear on how they are determining which products are predominantly targeted to the Medicare population, or whether a drug would actually be negotiated by Medicare. As stated before, facets to products e.g., pricing, clinical trial and other clinical evidence generation efforts, are generally not designed against sources of insurance. How will ICER manage the significant uncertainty in determining which drugs will ultimately be selected and when? Finally, ICER should solicit input from providers, patients, and manufacturers when selecting comparator drugs. Manufacturers have significant understanding of the medicine, disease, and what the medicine may replace in patient care. It also provides a more efficient process, and improves scientific credibility to design more holistic stakeholder engagement from start to end.

3.3 Quantifying Additional Dimensions of Value

It remains important that a medicine's benefit should include a range of outcomes of relevance to patients, carers and societies, and cover the long-term impact of those medicines. Whilst survival in a health state and the impact of that health state on a patient are critical, quality adjusted life years (QALYs) typically don't measure the patient's own perspective on their health state and health related quality of life (HRQoL), but a societal view of that health state. Therefore, measures should also include (but not be limited to) impact on domains of HRQoL, symptoms, independence, and patient preferences based on route or frequency of administration, which are not typically captured in standard health state utility instruments. Within a societal perspective, additional value elements such as impacts on population health equity, impacts on caregiver HRQoL, and economic impacts outside the healthcare system should also be considered.

3.4 Health Benefit Price Benchmarks

QALYs combine quality and length of time but have the potential to be discriminatory to individuals in poorer health states. Whilst equal value of life years gained (evLYG) may help address these shortcomings, it just applies a general health state utility value to all health states in any life-years gained. For example, evLYG would equally value two new treatments that both extend life by one year, even if one treatment has the differentiating factor of also significantly improving quality of life (or health state utility) during that added year of life. Thus, while addressing one limitation with QALYs it introduces new ones. Further, evLYG has the same limitation as QALYs in that it does not capture the true benefits of a medicine on both quality of life, symptom improvement, tolerability and life extension from a patient perspective.

Regarding the two scenario analyses for high-impact single or short-term therapies that ICER proposes, both of these are arbitrary values and impose a system that runs counter to how other medicines are evaluated, with an effect of focusing on lowering medicine prices. More robust scientific evidence should be applied before incorporating these as standard into the VAF. Of more relevance would be considering payment models and apportioning cost to a patient's insurers over the long time they benefit from such innovations; this would help to spread the cost

fairly amongst different plans so that the full cost does not land with the initial plan while benefits are concentrated in subsequent plans.

3.5 Other Changes

We support ICER's commitment to seek opportunities to use real-world evidence (RWE) within their assessments. RWE is especially valuable for reducing uncertainty in the evaluation of medicines for which trial readouts may take longer or those for early approvals.

A2 Topic Selection

We recommend that ICER work with manufacturers as part of this process for emerging therapies/drugs. Further, we support consideration of health disparities. Finally, we ask that ICER provide greater transparency regarding why they select topics and the influence of their members in these decisions.

A3 Stakeholder Engagement

We support ICER's commitment to patient involvement. We further offer that improvements to patient engagement opportunities would be beneficial to ensure patient perspectives are meaningfully considered. For example, ICER can solicit patient feedback on how they felt they had an impact on ICER's assessment and where it made a difference.

Thank you again for the opportunity to provide comment on the proposed changes to the VAF. If you have any questions about these comments, please contact Christine Ney at christine.ney@astrazeneca.com.

Kind regards,

Beth Hamilton
Global Vice President, Oncology Market Access and Pricing



Via Electronic Submission: publiccomment@icer.org

June 30, 2023

Steven D. Pearson, MD, MSc, FRCP President
Institute for Clinical and Economic Review 14
Beacon Street, Suite 800
Boston, MA 02108 USA

RE: Feedback on 2023 Value Assessment Framework Proposed Changes

Dear Dr. Pearson,

Bayer HealthCare Pharmaceuticals (Bayer) appreciates the opportunity to comment on the recently announced set of proposed changes to the Institute for Clinical and Economic Review's (ICER) methods and processes for conducting value assessments beginning in 2024.

Bayer is a global enterprise with core competencies in the Life Science fields of healthcare and agriculture with nearly 25,000 employees in 30 sites across the United States. Our products and services are designed to help the planet and people thrive and improve their quality of life. At the same time, we aim to create value through innovation and are committed to the principles of sustainable development and to our social and ethical responsibilities as a corporate citizen.

Our comments below address three crucial areas related to ICER's proposed changes.

I. Clinical trial demographic diversity, health equity, and relevant sub-population identification are critically important for meaningful value assessments.

Clinical trial diversity and health equity considerations

Bayer advances a culture of inclusion and diversity to drive innovative solutions. Inclusion and diversity play an important role in meeting and anticipating the needs of our customers and achieving our overall vision: Health for all, Hunger for none.¹ As such, Bayer is committed to the goal of inclusive clinical trials that represent the diversity required to address the needs of all patients, including ensuring appropriate participation from underrepresented racial and ethnic populations. To advance this goal, Bayer is working with healthcare stakeholders including clinicians, research scientists, health authorities, ethics committees, and partners in patient engagement to address barriers to clinical trial participation.² As ICER acknowledges in its proposed changes to its framework, driving meaningful change in this space requires "investment, transparency, accountability, and partnerships across key stakeholders." However, we are concerned that the inclusion of ICER-defined clinical trial diversity ratings in its assessments is premature and will not provide meaningful information to improve clinical trial diversity. Overcoming systemic barriers and improving clinical trial diversity will depend on multi-stakeholder, collaborative efforts including coordination with patient groups, life sciences companies, and the Food and Drug Administration (FDA) to develop evidence-based solutions. The FDA has initiated multiple efforts to improve clinical trial diversity,^{3,4,5} and is better positioned to guide and measure progress in this area. ICER's efforts should complement the FDA's guidance and activity in

//////////

June 30, 2023

Todd Williamson
Bayer U.S., LLC
Vice President
Data Generation and
Observational Studies
100 Bayer Blvd
Whippany, NJ 07981
Tel. +1 862.404.5418
Todd.Williamson@bayer.com
www.bayer.com

this space.

Further, Bayer is committed to participating in global health governance and working to achieve health equity and better access for all. ICER proposes very modest methods adaptations related to improving the consideration of health equity in its assessments. While we support ICER's decision to include two health equity-related voting panel questions and appreciate ICER's effort to integrate health equity into topic selection, we do not feel that ICER has proposed any significant changes to its methodological processes that will meaningfully account for health equity considerations in its assessments.

Sub-population analyses

Bayer appreciates ICER's proposed changes related to acknowledging and including subpopulations in its value assessments. Moving forward, it will be essential to engage stakeholders, particularly manufacturers, to identify relevant subpopulations to inform more comprehensive assessments. We appreciate ICER's proposal to consider race, sex, and age as presumptive subpopulations for every review, but strongly encourage ICER to include additional subpopulations in its assessments when relevant.

- ***Recommendations:***

- Improving clinical trial diversity will depend on multi-stakeholder, collaborative efforts to overcome systemic barriers. ICER's proposed inclusion of clinical trial diversity ratings in its assessments is premature, limiting the relevance and strength of such analyses to inform decision-making. Instead, we recommend ICER better address health equity within its methods and process by integrating mechanisms for engagement and input by patients and caregivers to ensure a diverse set of populations and viewpoints are represented and incorporated within ICER's assessments.
- Relevant sub-populations necessarily change by disease state and product(s) and therefore there cannot be a one-size-fits-all approach to sub-population identification. ICER should engage with all stakeholders, including manufacturers, to identify and consider all relevant subpopulations (eg, disability status, pediatric populations) in its assessments.

II. ICER's value assessments should adhere to current methodologic best practices.

To advance meaningful and rigorous value assessments, ICER's analyses must align with methodologic best practices related to inclusion of the societal perspective, accounting for additional dimensions of value, as well as calculating cost-effectiveness thresholds and its shared savings scenarios.

Inclusion of the societal perspective

ICER has repeatedly received comments from stakeholders to incorporate the societal perspective as a co-base case, as doing so captures the overall cost impacts and public benefit generated by assessed interventions and is superior to the healthcare perspective in capturing outcomes important to the patient community including productivity, caregiver burden, insurance value, and spillover effects. Elevating the societal perspective to a co-reference case aligns with recommendations from HTA experts, including the Second Panel on Cost-effectiveness in Health and Medicine.⁶ Despite HTA experts' recommendations and strong stakeholder consensus that ICER should consider the societal perspective as a co-equal base case, ICER does not propose to amend its criteria for promoting the modified societal perspective to a co-base case. This decision is out of step with best practices for value assessment. Moreover, historically, ICER has inconsistently applied the modified societal perspective, even in circumstances in which the assessed intervention met ICER's criteria.^{7,8,9}

- **Recommendation(s):**

- ICER should consider the societal perspective as a co-equal base case, in alignment with best practices for value assessment.
- While we strongly recommend that ICER consider the societal perspective as a co-equal base case, at a minimum, ICER should ensure consistent application of its current criteria in the event that no criteria change is made.

Inclusion of additional dimensions of value

ICER's value assessments should rely on a comprehensive, patient-focused definition of value. Reliance on a narrow set of methodological inputs may result in assessments of treatment value that are misaligned with patient needs and preferences, limiting the appropriateness of their findings for informing decision-making. A growing body of empirical evidence supports the quantitative inclusion of additional dimensions of value that have historically been excluded from traditional cost-effectiveness analyses including productivity, value of hope, real option value, among many others.^{10,11,12,13,14} Incorporating these value dimensions aligns with recommendations from patient groups, researchers, and health economists to advance more comprehensive and patient-focused value assessments.

Despite these recommendations and the growing body of empirical evidence and new methodological approaches to support quantitative inclusion of additional dimensions of value, ICER proposes to continue to only qualitatively capture these considerations. Notably, ICER also concurrently proposes to considerably narrow the discussion of additional value elements in its appraisal committee deliberations, now including only votes on unmet need, caregiver quality of life, and health equity considerations. Appraisal committee votes previously incorporated key patient-focused dimensions of value related to treatment complexity, lifetime impact, and mechanism of action. ICER's proposal to considerably narrow the discussion of additional value elements is a step backward in capturing a complete representation of treatment value. If ICER's proposed changes are implemented, it will not only continue to exclude important value elements quantitatively, but it will also place new limitations on even their qualitative inclusion in its assessments.

- **Recommendation(s):**

- ICER should not eliminate the value elements it included in the past such as mechanism of action, complexity, lifetime impact, etc. ICER should include these elements in a meaningful and quantitative manner.
- As previously noted in earlier communications with ICER:
 - We reemphasize our recommendation that elements of value, such as those captured by ICER in its new "Benefits Beyond Health" and "Special Ethical Priorities" sections of the report, should be summarized in a table or graphic side-by-side with the comparative effectiveness, long-term value, and short-term affordability estimates as part of the Report-at-a-Glance.
 - This format would allow readers to readily view and interpret key determinants of value of an intervention as a whole rather than in silos.
 - Any summaries must also be inclusive of the full range of values estimated under varying assumptions to ensure full transparency of the uncertainty underlying them.
- Further, ICER should consider the growing body of empirical evidence supporting the quantitative inclusion of additional dimensions of value to ensure that changes translate meaningfully to more patient-focused assessments, including quantitative incorporation of patient-identified value elements.

Calculating cost-effectiveness thresholds

In its proposed methods adaptations, ICER states that it will “pursue further discussion with academic experts and stakeholders to consider whether the Health Benefit Price Benchmark (HBPB) Price range should be shifted to \$50,000 to \$100,000 per QALY or evLYG in order to better reflect the true opportunity costs experienced by many Americans.” Moreover, ICER suggests accounting for the opportunity cost perspective with a top threshold of \$104K/QALY, stating that such a threshold is a necessary counterweight to quantitatively incorporating additional value elements such as benefits for new interventions. However, this assertion is unfounded, as ICER does not quantitatively account for additional value elements.

Bayer is deeply concerned by the inclusion of this language, as lowering the current cost-effectiveness thresholds is out of sync with US market realities and such action is not supported by scientific evidence. It is well-established in the literature that cost-effectiveness thresholds vary by disease state and severity, indicating a wide range of appropriate ranges. Research shows that US analyses increasingly cite a range of \$100,000-\$150,000/QALY, with disease specific analyses (e.g., cancer) referencing even higher thresholds.¹⁵ Further, ICER has not updated its cost-effectiveness thresholds since they were initially introduced, and therefore they do not account for recent changes in the US economy, including rising inflation and increases in US gross domestic product (GDP). Moreover, use of a cost-effectiveness threshold of up to three times per capita GDP has been widely cited in the literature;^{16,17} ICER’s application of this methodology would result in a much higher threshold. To better reflect US market realities, ICER should consider dynamically increasing its thresholds to account for changes in inflation and growth in the US economy.

- **Recommendation(s):**

- ICER should not lower its cost-effective thresholds, as doing so would be out of sync with US market realities and would result in limited, inappropriate value determinations. Should ICER choose to update its thresholds, it should increase them to account for inflation and growth in the US economy.

Shared savings scenarios

ICER states it “will continue to consider” the results of its shared savings approach, which it created for its single and short-term therapies (SSTs) methods adaptations, to determine HBPBs for any “other treatments with relevant and substantial potential cost-offsets.” Bayer strongly disagrees with ICER’s codification of these analyses, as they do not adequately reflect the value of assessed interventions and are not supported by empirical evidence or scientific justification. Instead, these scenarios rely on ICER-developed methods; the cost offset cap of \$150K was arbitrarily selected because it aligns with the top of ICER’s value-based price threshold and is not adjusted to reflect actual disease-related cost offsets, which often far exceed \$150K per year.¹⁸ As a result, application of these methods significantly underestimates real-world cost offsets and should not be used to calculate HBPBs for SSTs or any other treatments. For these reasons, inclusion of these scenarios underestimates treatment value, which may perpetuate the use of inefficient and expensive standards of care and disincentivize future development of innovative therapies.

- **Recommendation(s):**

- ICER should not apply its shared savings scenarios in any of its assessments (SST or otherwise) due to their reliance on limited methods and potential to underestimate the value of assessed interventions.

III. Prioritize stakeholder feedback and engagement

Although ICER states that the purpose of its framework is to “*form the backbone of rigorous, transparent evidence reports that, within a broader mechanism of stakeholder and public engagement, will help the US evolve toward a healthcare system that provides fair pricing, fair access, and a sustainable platform for future innovation*” the elimination of the open input period, the compression of the public comment period, and the shortened length of stakeholder comments call ICER’s adherence to this purpose into question. Meaningful, patient-focused assessments require robust multi-stakeholder engagement; failure to provide such opportunities, and meaningful incorporation of stakeholder feedback will result in weaker, narrower assessments of value that have limited applicability to US healthcare decision-making.

Bayer appreciates ICER’s efforts to enhance its Patient Engagement Program, as such changes could represent a positive step forward for ICER’s engagement of patients and caregivers in its assessments. However, steps should be taken to ensure that changes translate meaningfully to more patient-focused assessments, including quantitative incorporation of patient-identified value elements.

- **Recommendation(s):**

- ICER must recommit to prioritizing stakeholder feedback to rebuild transparency and credibility of its engagement process with stakeholders.
- We would also encourage and be supportive of an independent evaluation of the effectiveness of the Patient Engagement Program and its impact on assessment results.
- ICER’s final reports and Reports-at-a-Glance should include more user-friendly and lay-language the clearly outlines the patient’s perspective.

###

We greatly appreciate the opportunity to provide feedback on the *2023 Value Assessment Framework Proposed Changes* and look forward to working with ICER to ensure access to needed medications and improved patient care.

Kind regards,

Todd Williamson, MSc
Vice President, Data Generation & Observational Studies,
Bayer HealthCare Pharmaceuticals Inc.

References:

¹ Bayer. Inclusion & Diversity at Bayer. Accessed June 27, 2023. <https://www.bayer.com/en/commitments/inclusion-diversity-at-bayer>

² Bayer. Clinical Trials. Accessed June 27, 2023. <https://clinicaltrials.bayer.com/>

³ U.S. Department of Health and Human Services. Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry. April 2022. Accessed June 27, 2023. <https://aboutblaw.com/601>

⁴ U.S. Food and Drug Administration. FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials. April 20, 2022. Accessed June 27, 2023. <https://www.fda.gov/news-events/press-announcements/fda-takes-important-steps-increase-racial-and-ethnic-diversity-clinical-trials>

⁵ U.S. Food and Drug Administration. Patient Engagement Collaborative. June 13, 2023. Accessed June 27, 2023.

<https://www.fda.gov/patients/learn-about-fda-patient-engagement/patient-engagement-collaborative>

⁶ The Second Panel on Cost-Effectiveness in Health and Medicine. Recommendations on perspectives for the reference case. In: Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, eds. *Cost-Effectiveness in Health and Medicine*. 2nd ed. New York: Oxford University Press; 2017.

⁷ Institute for Clinical and Economic Review. Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value. December 22, 2022. https://icer.org/wp-content/uploads/2022/05/ICER_Hemophilia_Final_Report_12222022.pdf

⁸ Institute for Clinical and Economic Review. Valoctocogene roxaparvovec and emicizumab for hemophilia A without inhibitors: effectiveness and value. November 2020. https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia-A_Final-Report_112020.pdf

⁹ Institute for Clinical and Economic Review. Special Assessment of Outpatient Treatments for COVID-19: ICER Final Evidence Report and Meeting Summary. May 10, 2022. Accessed June 27, 2023. https://icer.org/wp-content/uploads/2021/08/ICER_COVID_19_Final_Evidence_Report_051022.pdf

¹⁰ Ma S, Olchanski N, Cohen JT, Ollendorf DA, Neumann PJ, Kim DD. The Impact of Broader Value Elements on Cost-Effectiveness Analysis: Two Case Studies. *Value Health*. 2022 Aug;25(8):1336-1343.

¹¹ Mattingly, T.J., Slejko JF, Onukwugha E, Peretto EM, Kottlil S, Mullins CD. Value In Hepatitis C Virus Treatment: A Patient-Centered Cost-Effectiveness Analysis. *Pharmacoeconomics*. 2019;38(2):233-242.

¹² Li M, Basu A, Bennette C, Veenstra D, Garrison LP. How Does Option Value Affect the Potential Cost-Effectiveness of a Treatment? The Case of Ipilimumab for Metastatic Melanoma. *Value Health*. 2019 Jul;22(7):777-784.

¹³ Reed SD, Yang J, Gonzalez JM, Johnson FR. Quantifying Value of Hope. *Value Health*. 2021 Oct;24(10):1511-1519.

¹⁴ dosReis S, Butler B, Caicedo J, Kennedy A, Hong YD, Zhang C, Slejko JF. Stakeholder-Engaged Derivation of Patient-Informed Value Elements. *Patient*. 2020;13(5):611-621.

¹⁵ Neumann PJ, Kim DD. Cost-effectiveness Thresholds Used by Study Authors, 1990-2021. *JAMA*. 2023 Apr 18;329(15):1312-1314.

¹⁶ Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S Thresholds for the cost-effectiveness of interventions: alternative approaches. *Bull World Health Organ*. 2014;93(2):118-124.

¹⁷ Griffiths M, Maruszczak M, Kusel J. The who-choice cost-effectiveness Threshold: a Country-level analysis of changes over time. *Value Health*. 2015 May; 18(3); PA88.

¹⁸ Institute for Clinical and Economic Review. Adapted Value Assessment Methods for High-Impact “Single and Short-Term Therapies” (SSTs). November 12, 2019. Accessed June 27, 2023. https://icer.org/wp-content/uploads/2020/10/ICER_SST_FinalAdaptations_111219.pdf



Biotechnology Innovation Organization
1201 New York Avenue NW
Suite 1300
Washington, DC, 20005
202-962-9200

June 30, 2023

Via Electronic Delivery

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
14 Beacon Street, Suite 800, Boston, MA 02108

RE: Proposed Adaptations to the ICER Value Assessment Framework

Dear Dr. Pearson:

The Biotechnology Innovation Organization (BIO) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER's) proposed updates to its value assessment framework (VAF).

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than thirty 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 yield not only improved health outcomes, but also reduced health care expenditures due to fewer physician office visits, hospitalizations, and surgical interventions.

BIO represents an industry that is devoted to discovering—and ensuring patient access to—innovative treatments. Accordingly, we monitor and engage in discussions around the value of innovative therapies to ensure that patient access and the need to sustain future innovation are appropriately considered by public payors, policymakers, and government regulators in these dialogues. Of foremost concern to BIO is that this proposed value framework (and any other value framework that may be used by such stakeholders) appropriately captures the long-term benefits of therapeutic interventions, includes model inputs that are evidence based, and ensures that the results of the analysis are meaningful to patients, their caregivers, and their healthcare providers. Additionally, we are concerned that the short comment period provided for this value framework update is inadequate, limiting the ability of key stakeholders to respond. This is in tandem with a more restrictive comment period than for prior framework revisions. These factors create significant barriers for ICER to obtain meaningful input.

Our concerns with this VAF are outlined below:

ICER must incorporate societal value into its framework

We are disappointed to see that ICER continues to resist routinely incorporating the societal value of a given treatment into its Health Benefit Price Benchmark (HPBP) framework. The proposed VAF states; “On rare occasions, ICER will judge that the modified societal perspective findings should be included in some way in framing the HPBP.”¹ It is unclear what ICER means by “on rare occasions” and how they will define those; however, societal benefits should be included for all assessments of value.

Such a move is confounding; ICER purports to aim to capture the full value of treatments in what it terms as “rigorous, transparent evidence reports,” but will deliberately blind itself to information that can augment these analyses and make the reports more comprehensive.² Moreover, the lack of definitions and clarity in the proposed framework is striking. We are concerned that with these murky criteria, there can be bias in selections and modelling outcomes.

Therapies have greater benefits to society beyond the immediate impact on a patient. Long term, treatments reduce mortality and morbidity, as well as improving a patient’s and caregiver’s overall quality of life. Moreover, treatments also improve the quality of life and overall health for caregivers as well, such as increased productivity and decreased absenteeism. For example, 34 percent of caregivers for patients with cystic fibrosis (CF)—a disease that severely damages the lungs and digestive system—suffer from clinical depression. And caregiver burden contributes to the overall disease cost, offering an additional financial benefit that the framework neglects to account for.³ The VAF as proposed (as well as currently constituted) continues to ignore these holistic benefits and various cost offsets of biopharmaceutical therapies. In addition to CF, the impact of treatments on caregiver and patient quality of life is also particularly true for advanced therapy medicinal products (ATMPs), such as one-time cell and gene therapies. Ultimately, caregiver and patient quality of life impacts are significant in many conditions, and must be measured. By ignoring societal benefits, ICER ignores elements of value that patients have deemed important, making the VAF lacking in patient centricity.

Indeed, ICER’s reports have been criticized for an uneven application of the social perspective. In a June 2023 report from the Institute for Patient Access (IfPA), it was found that ICER frequently deviated from its own commitment of applying a modified societal perspective in its assessments. The report also added that in updating its VAF, ICER should include the societal benefits of a treatment and “prioritize the consistent inclusion of the societal perspective.” The IfPA concluded its report, writing; “ICER is failing to adhere to widely accepted best practices for cost-effective analysis and value assessment that have been echoed by stakeholders, including patients.”⁴ Another study from the Center for the Evaluation of Value and Risk in Health (CEVR) said that organizations such as ICER infrequently

¹ Proposed VAF Changes at Pg. 15

² Proposed VAF Changes at Pg. 1

³ Neri, Luca, Vincenzina Lucidi, Paola Catastini, and Carla Colombo. “Caregiver burden and vocational participation among parents of adolescents with Cf.” Wiley Online Library. *Pediatric Pulmonology*, March 2016. <https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.23352>.

⁴ Institute for Patient Access. June 2023. *How Overlooking Societal Impact Undermines ICER’s Cost-Effectiveness Assessments*, available at https://instituteforpatientaccess.org/wp-content/uploads/2023/05/IfPA_ICER_SocietalPerspectivePaper_May-2023.pdf.

incorporated the societal perspective, even though doing so would “more appropriately reflect the full consequences of using new technologies.”⁵

We question ICER’s insistence in continuing to omit the social perspective. Instead of taking the totality of a given therapy’s impacts and benefits over time, the VAF instead shortchanges the value of these biopharmaceutical innovations and benefits they confer to patients and society. This has a negative impact on patient outcomes and can result in additional costs for the overall system rather than the intended savings.

Any discussion of value assessment frameworks must be patient and caregiver centered

Patients are at the core of everything we do in the biopharmaceutical sector and must also be at the core of any value assessment dialogue. The standard in the implementation and usage of value assessment tools must be to improve health equity and to remove barriers to patient access, and not to erect further barriers. We are encouraged by the expansion of a patient engagement program and the proposed formalized small-group patient and caregiver discussions and proposal for a Patient Council. However, it is important to ensure that the patients selected to provide input through these mechanisms reflect the patients who may actually be treated. ICER should provide further clarity on its selection process.

However, without any substantive changes to the framework to incorporate societal value, the VAF cannot accurately capture patient and caregiver impacts in its outputs. We believe the current approach is especially flawed with respect to rare and genetic diseases, as the framework is too narrowly focused on effectively capturing the value of the medicine while undervaluing patients’ suffering from serious and life-threatening rare diseases. In only attempting to capture short-term benefits and costs, the VAF has the potential to be interpreted and applied inappropriately by public and private payors to inhibit patients’ access to therapies that can improve and enhance their lives. Delaying or denying patient access discourages longer-term utilization, which can not only negatively impact health outcomes, but result in missed opportunities to contribute to decreasing overall healthcare expenditures through the avoidance of costly hospitalizations, surgical interventions, physical office visits and other intensive supportive care or medical interventions. This is problematic because we know that payers rely on ICER to make coverage decisions. In fact, in 2016, 49 percent of payers reported that ICER recommendations influenced their formulary decisions; in 2018, that number rose to 78 percent. Reliance on incomplete assessments has the potential to have devastating consequences for patients, especially if there are not many treatment options to begin with.

This can result in evaluations that are less likely to deem orphan drugs cost-effective, for example, with the potential to restrict access to orphan drugs for patients with rare diseases.⁶

Additionally, we believe the absence of a material impact of a therapy’s “contextual considerations” on ICER’s value-based price metric significantly limits the report’s applicability to real world pricing and

⁵ Breslau RM, Cohen JT, Diaz J, Malcolm B, Neumann PJ (2023). A review of HTA guidelines on societal and novel value elements. *International Journal of Technology Assessment in Health Care*, 39(1), e31, 1–7 <https://doi.org/10.1017/S026646232300017X>

⁶ “ICER’s Growing Influence on Payer Decision Making: The Impact of ICER Assessments on Market Dynamics and Patient Access.” Xcenda, November 2, 2020. <https://www.xcenda.com/insights/hta-q-winter-2020-icer-payer-decision-making>.

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

In value assessment, these contextual and societal considerations must be considered, because without them, patients and caregivers are left in the lurch and not wholly considered, with devastating impacts for them. In fact, the heterogeneity of rare and genetic diseases makes it challenging to capture consequential outcomes that can be accurately generalized to the entire patient population and therefore, incorporating patient and societal considerations is essential for developing an accurate assessment of a drug for these type of diseases. For example, it can be challenging to enroll a sufficient number of patients in clinical trials for rare diseases given small patient numbers, uneven distribution of disease across populations, and heterogeneity of diseases. It is similarly challenging to design clinical trials for rare disease populations given difficulties designating an appropriate comparator, validating novel endpoints, and obtaining sufficient data from small patient populations. By using an incomplete assessment that neglects to include additional, more holistic factors, the VAF is itself incomplete and therefore, not a reliable assessment for use.

The proposed VAF does not consistently apply the patient perspective, with only some criteria proposed for when patients should be consulted in the assessment of a treatment. As the IfPA report mentioned earlier shows, ICER does not always apply its own criteria consistently in its reports. We urge ICER develop a formal mechanism to capture the patient’s perspective when considering a therapy’s value to be used across all value assessments and qualify it in a meaningful way. The Innovation and Value Initiative (IVI) recently published a report that helps in establishing a framework for patient-centered value assessment, with some key recommendations that ICER would benefit from incorporating into its VAF.⁷

The concept of “value” is not a static concept and will evolve over time with real world evidence and especially because of the experiences of clinicians and patients. We believe more must be done to consistently incorporate patients and caregivers from the ground up in this proposed VAF, with a concerted effort towards including and centering patient voices. In doing so, ICER will be better able to continue to keep up with the evolving concept of “value.”

The proposed framework needs to acknowledge when its outputs are missing key elements or are otherwise unreliable

We remain concerned that ICER’s reports do not appropriately convey when – because of methodological or other reasons – their results may not be applicable to real-world pricing and coverage decisions. The science and methods of value measurement are constantly being deliberated and refined. Yet often ICER’s reports present results as if the science of value measurement were static. For

⁷ Malik E, Bright J, Ridley E, Cope E, Edmunds M (2023). A Research Framework to Understand the Full Range of Economic Impacts on Patients and Caregivers. Innovation and Value Initiative and AcademyHealth. https://thevalueinitiative.org/wp-content/uploads/2023/05/May-2023-Economic-Impacts-Framework-Report_FINAL.pdf

example, although ICER claims to understand the importance of taking the long-term perspective on a treatment's benefits and costs, current limitations in methods often preclude adequate modeling of this perspective at the time of ICER's assessment. The lack of cost-effectiveness methods that account for the long-term perspective in certain disease states necessarily limits the value of ICER's results to readers – and particularly those health care professions who may make clinical or benefit determinations based on ICER's results.

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

ICER must further address the deficiencies of the quality adjusted life year (QALY)

We continue to object to the use of the QALY as the fundamental metric of ICER's review. While we appreciate ICER's recognition of the QALY's shortcomings in developing the equal value of life year gained (evLGY) metric, we believe more must be done to communicate concerns around QALYs and how their use can impede the goals of personalized medicine. While we appreciate that the evLGY metric is an attempt to advance the methodology, these metrics too suffer from the same issues as QALYs, and they are similarly problematic as they limit the value of interventions that both extend life and improve the quality of life.

QALYs and QALY-like measures are highly subjective and assign different values to different patients in a manner that discriminates against those with disabilities and the elderly. There is a need for value assessment, but such value assessment must be robust and not devalue the lives of certain patients and populations. In assessing its VAF, ICER should move away from generic, flawed measures like QALYs, and instead seek a more holistic approach in its methodology that centers on patients.

We thank you for the opportunity to register our thoughts and concerns on this topic, and look forward to future discussions. Please do not hesitate to contact us with any questions at (202) 962-9200.

xxxxx

Crystal Kuntz
Senior Vice President,
Healthcare Policy and Research

June 30, 2023

Steven D. Pearson, M.D., M.Sc. FRCP President
Institute for Clinical and Economic Review

RE: Call for Public Input on ICER's 2023 Value Assessment Framework Proposed Changes

Submitted electronically via: publiccomments@icer.org

Dear Dr. Pearson,

Bristol Myers Squibb Company (BMS) appreciates the opportunity to provide input on ICER's proposed changes to your Value Assessment Framework (VAF). BMS also supports the comments submitted by BIO, NPC, and PhRMA.

At BMS, we are inspired by a single vision—transforming patients' lives through science. We are in the business of breakthroughs—the kind that transform patients' lives through lifesaving, innovative medicines. Our talented employees come to work every day dedicated to the mission of discovering, developing, and delivering innovative medicines that help patients prevail over serious diseases. We combine the agility of a biotech with the reach and resources of an established pharmaceutical company to create a global leading biopharma company. In oncology, hematology, immunology, and cardiovascular disease—with one of the most diverse and promising pipelines in the industry—we focus on innovations that drive meaningful change.

BMS acknowledges the importance of promoting a rigorous, comprehensive, and inclusive approach to value that aligns with best practices in value assessment. With this approach in mind, we urge ICER to consider the following comments and recommendations, briefly discussed in this letter:

- BMS supports clinical trial diversity, but we are concerned with ICER's proposals to:
 - a) benchmark diversity for conditions with “unreliable” epidemiology to national demographics and
 - b) measure multinational trial diversity based on only US participants.
 - We are concerned with ICER's proposed *a priori* list for subpopulation analysis and presumed focus on clinical trial evidence versus real world data.
 - BMS recommends ICER expand assessments to include the broader impact of medicines on society to help ensure greater recognition of holistic value and rewards for innovation.
 - We recommend ICER consult relevant experts to establish clearer criteria for use of dynamic pricing scenarios, considering the value of generic entry and multiple incident cohorts.
 - While we support consideration of disease severity and health equity, we are concerned with the mechanisms ICER proposes to incorporate these considerations (QALY shortfall severity modifier and HIDI) and recommend further consultation with patients and health care providers to establish the appropriate framework for severity.
 - We believe a cost-effectiveness threshold based on either QALYs or evLYG is ill-suited for application in the US and around the world. We urge ICER to appropriately contextualize cost effectiveness analysis (CEA) as merely one aspect of a broader assessment of value and strongly disagree with ICER's consideration to lowering HBPB ranges.
 - While we support ICER considering RWE, we are concerned with collection of this evidence through a subscription-based platform.
-

Comparative Clinical Effectiveness: Clinical Trial Diversity and Subpopulation Analyses

As an inclusive, patient-centered biopharmaceutical company, BMS is committed to health equity and ensuring everyone has a *fair and just opportunity* to achieve optimal health outcomes. In order for us to better serve diverse populations, maintaining and increasing clinical trial diversity is paramount. Our science and research will better reflect the patient populations most impacted by the diseases we treat - ultimately helping to improve treatment and patient outcomes for underserved communities, with narrowing racial gaps in care as our starting point. BMS continues to identify and activate clinical trial sites in racially and ethnically diverse geographies in the U.S. while strengthening our efforts towards thinking about clinical trials from design. We understand that there is no one-size-fits-all solution—we must employ a combination of adaptable, tactical approaches with continuous reflection and modification to make progress against our goals. We are confident that by breaking down the barriers to clinical trial participation with thoughtful and long-term approaches, we will effect real change and deliver on our patient-focused R&D mission.

While BMS appreciates ICER’s desire to promote clinical trial diversity, we have concerns with ICER’s proposed rating system, particularly on the consideration of conditions with limited disease-specific prevalence estimates and the proposed treatment of multinational trial populations. ***We recommend that ICER not benchmark clinical trial participation to national population demographics for small patient populations where they may consider epidemiology data “unreliable.” We also recommend that ICER consider clinical trial diversity at a worldwide level for multinational trials rather than limiting it to patients enrolled in the US.*** We note that other organizations such as Bioethics International and their Good Pharma Scorecard¹ are already measuring clinical trial diversity and suggest that ICER consult with these organizations that are better equipped to assess trial diversity in a way that is meaningful to the relevant patient populations.

BMS supports ICER’s proposal to include a scientific rationale for evaluating selected subgroups in the scoping document for future assessments; however, we are concerned with the proposed a priori list and presumed focus on clinical trial data versus real world evidence. We believe there is a risk that many of the proposed subgroup analyses will not have been pre-specified in the statistical analysis plan for the pivotal trial(s). For medications that have been recently approved, pivotal RCT gives clues into which subpopulations should be studied further, but these trials do not typically have sufficient subpopulation representation for meaningful comparisons. Extensive post-hoc subgroup analyses increase the risk of Type I errors (false positives), reporting clinical findings that may be due to chance alone. These *a priori* subgroup analyses may also contradict the FDA, who are ultimately responsible for evaluating the overall risk-benefit of new medicines. ICER’s publication of their *a priori* analyses could potentially lead to sub-optimal treatment decisions by those not aware of the issues of unplanned post-hoc subgroup analyses.

Long-Term Cost Effectiveness: Perspective in Economic Models, Dynamic Pricing Scenario, Quantifying Additional Elements of Value and Health Benefit Price Benchmarks

BMS appreciates ICER’s proposal to consider productivity for patients and caregivers as part of their reviews. The productivity impact to patients should include both formal and informal labor, household production, and leisure time, and we believe it is also critical to consider caregivers’ time and health impacts. ***When direct data is not available, we support a validated indirect approach to assess productivity impacts with assumptions that are aligned with patients and caregivers who are the most knowledgeable about the burden of the patients’ condition and treatment.***

Both the ISPOR Value Flower and the 2nd Panel on Cost-Effectiveness in Health and Medicine articulated elements of value that go beyond the impact of a medicine on the healthcare sector.^{2,3} In addition to impacting length and quality of life, effective medicines can help patients and caregivers to get back to work, provide a bridge to future medicines, improve the efficiency and quality of care in healthcare systems, inspire innovation in other treatment areas, and improve equity in the population, as well as the impact upon education, the legal system and other sectors of society – and so much more. The value of COVID-19 vaccines was not limited to the reduced incidence of disease and lives saved – they allowed society to reopen, supported innovation in oncology and rare diseases, and inspired efficiencies in other areas of healthcare.

However, even with the endorsement of leading academics and professional societies such as ISPOR, HTA bodies have considered these additional value elements as beyond their remit, while also considering the evidence used to support them as being of insufficient quality to change their mind. In turn, pharmaceutical manufacturers consider investment in generating evidence to support additional value elements as futile, given the stance of HTA bodies. As a result, these additional elements of value have rarely been incorporated into value assessments, even if they have the potential to impact incremental cost-effectiveness ratios or incremental patient benefit – as shown by COVID-19 vaccines and immuno-oncology medicines.

In this context, BMS welcomes ICER’s attempt to expand their perspective to assess the value of pharmaceutical intervention. ***We believe that expanding assessments to include the broader impact of medicines on society will help ensure greater recognition of their holistic value and translate to greater rewards for innovation.*** This will in turn act as an incentive to generate timely and fit for purpose evidence on additional elements of value beyond those traditionally captured within a healthcare perspective.

BMS generally supports consideration of dynamic pricing scenarios in CEA to acknowledge changes in cost over a medication’s lifecycle, including reductions from lower-priced generic competitors. In fact, 90% of prescriptions in the United States are for generic drugs.⁴ While we see an opportunity to consider lifecycle pricing in future analyses, we believe more research is needed to understand the strengths and limitations of underlying methods. We anticipate a need for case-by-case assessments to appropriately consider such scenarios, including but not limited to the applicability of potential future compelled CMS price setting from the so-called “negotiation” provisions of the Inflation Reduction Act. ***We recommend ICER convene a panel of academic experts to further assess methods and establish clearer criteria for when and how dynamic pricing analysis should be considered, including consideration of the value that generic entry brings over the course of time and the manner of assessing such value.***

Using a single cohort for dynamic pricing scenario CEA is likely to lead to inaccurate estimates of the cost-effectiveness of many new drugs that will be consumed over extended periods of time. Recent case studies exploring dynamic real world pricing data demonstrated marked improvement in the ICERs of successive cohorts compared with the initial single cohort.⁵ ***If dynamic drug pricing scenario analysis is undertaken, we propose that multiple incident cohorts are modelled as the default.***

ICER proposes to consider additional elements of value on a qualitative versus quantitative basis, citing methodological issues related to double counting and the inability to measure related opportunity costs. ***BMS recommends that ICER conduct further research in this area because while there is a longstanding notion that inclusion of novel (non-traditional) dimensions of value leads to double counting, the supporting evidence for this assumption is sparse at best.*** In the absence of rigorous research, ICER presumes the “first counting” has sufficiently and appropriately captured the full and long-term benefit of an intervention. Moreover, additional research is required to evaluate

methodologies to identify, measure (when measurable) and incorporate the impact that an intervention has on these additional dimensions of value. As an example, while a few methodologies exist to account for some value dimensions (e.g., productivity), other dimensions suffer from lack of research on appropriate methodologies (e.g., family spillovers).

BMS generally supports the rationale behind ICER's proposed introduction of a severity modifier that would be taken into consideration alongside the cost and clinical effectiveness evidence. However, anchoring the proposed severity modifier to an evLYG framework means the adoption of all methodological limitations associated with QALY highlighted in the literature over the last few decades. Simply put, most methodological and ethical limitations of the QALY (e.g., health equity, measurement of health states, non-health effects, severity etc.) still apply to the evLYG.⁶ Moreover, in the real world, a QALY/evLYG (or associated shortfall) does not define whether a condition is considered severe. Anchoring the severity modifier to the evLYG framework does not establish a common understanding of what constitutes a severe condition. ***We recommend ICER assess severity by a broad range of characteristics and input from patients and health care providers, potentially with the use of systematic tools and methods on disease severity indices.***

BMS is encouraged by ICER's recognition that prevalence inequality is an important driver of overall impact on health inequality, requiring real world evidence, and hence moving away from the narrow focus on inclusive RCTs and subgroup analysis thereof to provide evidence about subgroup differences in treatment effect on the intervention groups (which are usually small and not the most important driver of health inequality impact). Nonetheless, the proposed HIDI measure seems overly simplistic and incomplete in two important ways: (1) it is limited to a two-group comparison looking at only one specific "subpopulation of interest" rather than looking at inequalities across a general population distribution, and (2) it only considers prevalence rather than making further calculations to determine the importance of prevalence in driving the overall impact on health inequality and analyzing trade-offs between cost-effectiveness and health inequality impact. The link between HIDI and CEA is missing.

ICER has proposed to codify approaches for framing CEA in relation to standardized Health Benefit Price Benchmarks (HBPB), suggesting that policymakers can consider an evLYG threshold as an alternative value-for-money benchmark. ***We believe a cost-effectiveness threshold based on either QALYs or evLYG is ill suited for application around the world, including in the US setting.*** 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 and that reflects the complexity of the US healthcare system, rather than apply methods derived from single-payer systems and uniform viewpoints of value.

Rou

BMS urges ICER to appropriately contextualize CEA as merely one aspect of a broader and holistic assessment of value. A 2021 Aspen Institute Advisory Panel recommended HTA economic evaluations be presented in a disaggregated format as it "...leaves the normative aspect of economic evaluation to the decision-maker rather than the organization producing the information. This approach provides flexibility in reporting and allows room to modify reports as new methods or outcomes measures are validated."⁸ We similarly recommend that ICER report economic information in a disaggregated format with proper contextualization that includes other novel elements of value discussed previously in this letter. ***BMS believes in rigorous and transparent scientific processes, including communication and dissemination, and thus recommends that ICER not only address uncertainty in a direct (i.e., quantitative) manner consistently and throughout its "Evidence Reports," but also upfront and***

transparently in its “Report-at-a-Glance” and any other communications it generates.

In addition to objecting to a standardized HBPB in general, BMS also strongly disagrees with ICER’s consideration of lowering HBPB ranges to \$50k to \$100k per QALY or evLYG. ICER states this shift is being considered to “better reflect the true opportunity costs experienced by many Americans” and points to negative effects of self-rationing from increasing insurance premiums and health care costs for the insured population. It is important to note that recent increases in insurance premiums and patient cost sharing may be attributed to non-pharmaceutical medical costs, employer elections in health insurance coverage, and tax policies encouraging enrollment in high-deductible health plans. Recent data from IQVIA suggests that pharmaceuticals represent only 14% of US healthcare spending.⁹ Employer health benefits survey data from Kaiser Family Foundation shows a 5-fold increase in average deductibles for employee single coverage from 2006-2022, with over 60% of workers having an annual deductible over \$1,000.¹⁰

Other Changes: ICER proposal on incorporation of real-world evidence (RWE)

BMS supports ICER continuing to seek opportunities to use RWE in its assessments. This evidence base can be incredibly informative and complementary to clinical trial findings, particularly 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 impact on the total cost of care. As interest in RWE continues to grow, the research methodologies and databases have become more sophisticated in providing highly reliable scientific data as part of the holistic body of evidence.

While we support ICER considering RWE submitted by manufacturers and other stakeholders, we are concerned with collection of this evidence through the ICER Analytics platform. This platform appears to require a subscription to ICER, and we believe stakeholders should be allowed to submit evidence through a mechanism that does not require a paid subscription.

BMS is taking this opportunity to comment on ICER’s proposed value assessment framework changes 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. We hope that ICER incorporates these considerations and recommendations into their value framework and processes.

Sincerely,



Anthony Barisano, PharmD
Vice President, US Health Economics and Outcomes Research

References

¹ Bioethics International, “Good Pharma Scorecard,” available at: <https://bioethicsinternational.org/good-pharma-scorecard/>

² Goring, S., Garrison, L., Jansen, J. P. & Higgs, A. H. 2022. Novel elements of the value flower: fake or truly novel? Value Outcomes Spotlight, 7, 34-39.

³ Neumann, P. J., Sanders, G. D, Russell, L.B., Siegel, J. E. & Ganiats, T.G. (eds). 2016. Cost-Effectiveness in Health and Medicine (2nd ed.). Oxford Academic.

⁴ US FDA, “Office of Generic Drugs 2021 Annual Report,” available at <https://www.fda.gov/drugs/generic-drugs/office-generic-drugs-2021-annual-report>

⁵ Schöttler MH, Coerts FB, Postma MJ, Boersma C, Rozenbaum MH. The Effect of the Drug Life Cycle Price on Cost-Effectiveness: Case Studies Using Real-World Pricing Data. Value Health. 2023 Jan;26(1):91-98.

⁶ Rand LZ, Kesselheim AS. Controversy Over Using Quality-Adjusted Life-Years In Cost-Effectiveness Analyses: A Systematic Literature Review. Health Aff (Millwood). 2021 Sep;40(9):1402-1410.

⁷ NICE, “NICE: 20 years of evidence-based decision making,” available at <https://indepth.nice.org.uk/20-years-of-NICE/index.html>.

⁸ USC Schaeffer Center – Aspen Institute Advisory Panel, “Health Technology Assessment in the U.S. – A Vision for the Future,” available at https://healthpolicy.usc.edu/wp-content/uploads/2021/02/Health_Technology_Assessment_in_the_U.S..pdf

⁹ IQVIA, “Drug Expenditure Dynamics 1995–2020: Understanding medicine spending in context,” available at <https://www.iqvia.com/insights/the-iqvia-institute/reports/drug-expenditure-dynamics>

¹⁰ Kaiser Family Foundation, “2022 Employer Health Benefits Survey,” available at: <https://www.kff.org/report-section/ehbs-2022-section-7-employee-cost-sharing/>



June 30, 2023

Steven Pearson, MD, MSc
President, Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

RE: ICER's proposed updates to Value Assessment Framework methods and procedures

Dear Dr. Pearson:

On behalf of individuals living with cystic fibrosis in the United States, we write to provide public comment on the Institute for Clinical and Economic Review's (ICER's) proposed updates to their Value Assessment Framework. We thank ICER for their continued work to include the complex topics of equity and diversity into their framework and share several comments and requests to further improve this effort.

About Cystic Fibrosis & the Cystic Fibrosis Foundation

Cystic fibrosis is a life-shortening genetic disease that affects nearly 40,000 children and adults in the United States. There is no cure for CF today. CF causes the body to produce thick, sticky mucus that clogs the lungs and digestive system, which can lead to life-threatening infections. Cystic fibrosis is both serious and progressive; lung damage caused by infection is irreversible and can have a lasting impact on length and quality of life. As a complex, multi-system condition, CF requires targeted, specialized treatment and medications. CF impacts people of all races and ethnicities. In 2022, 15 percent of people with CF living in the United States were identified as either Hispanic, Black, multiracial, Asian, or as other than White.¹

As a leader in the search for a cure for CF and an organization dedicated to ensuring access to high quality, specialized CF care, the Cystic Fibrosis Foundation supports the development of CF clinical practice guidelines and accredits 130 care centers and 55 affiliate programs nationally.

Below you will find several comments and requested changes to ICER's Framework that will allow future reports to more holistically consider new treatments and the value they may provide.

Clinical Trial Diversity

ICER will provide an overall diversity rating for the following demographic characteristics: race/ethnicity, sex, and age, specifically, adults aged 65 and older. To do this objectively and consistently across all ICER assessments, ICER will apply a new framework for

¹ 2022 Cystic Fibrosis Foundation Patient Registry Highlights Bethesda, Maryland ©2023 Cystic Fibrosis Foundation

evaluating clinical trial diversity based on the best practices described in our white paper on HTA methods and health equity.

We appreciate ICER's efforts to better recognize the importance of clinical trial diversity and incorporate it into the proposed changes to the Value Assessment Framework. However, the CF Foundation is concerned that ICER's proposed framework for evaluating clinical trial diversity and calculating a diversity rating may not be appropriate for every disease population—particularly those with demographic heterogeneity across multiple attributes.

Cystic fibrosis is broken into subpopulations based on CFTR variant or mutational class. These distinctions determine eligibility for and effectiveness of targeted small-molecule therapeutics, such as CFTR modulators; critically, the specific demographics listed by ICER (race/ethnicity, gender, age) may differ between each of these subpopulations. For example, the subpopulation of people with CF who are not eligible for CFTR modulator therapies based on CFTR variant is disproportionately composed of people of color.² Clinical trials targeting the subpopulation of people with CF with modulator-ineligible CFTR variants, including most clinical trials for CF gene therapies, would therefore need include a higher proportion of people of color with CF to achieve appropriate representation than the overall demographics of CF would suggest. In such cases, ICER's framework for evaluating clinical trial diversity by "comparing clinical trial participants to disease-specific prevalence" may result in an artificially inflated diversity rating regarding race/ethnicity.

It is not clear whether ICER intends to uniformly base its assessment of clinical trial diversity on the demographics (race/ethnicity, gender, age) of a disease population as a whole, or if there is flexibility to instead consider those demographics within the specific disease subpopulation most relevant to the clinical trial under consideration. We therefore ask for clarification from ICER on whether and how it will consider differences in disease subpopulations compared to the overarching disease population when calculating diversity ratings for clinical trials. If the proposed changes to the Value Assessment Framework do not support this type of analysis, we urge ICER to reconsider and perform revisions that reflect the potential for demographic variance in different distinct disease subpopulations and its relevance to properly assessing clinical trial diversity.

Subpopulation Analyses

To ensure that our reviews focus on evaluating the most relevant subpopulations, ICER will include an a priori list of the subpopulation of interest and the scientific rationale for evaluating these subpopulations in the scoping document and research protocol. ICER will rely on targeted literature reviews and interviews with patient and clinical experts conducted during scoping to identify the most relevant subpopulations.

ICER will consider race, sex, and age as presumptive subpopulations for every review. During topic scoping, we will evaluate the current evidence base and consult with clinical experts, patients, patient groups, and other stakeholders to investigate the relevance of subpopulations defined by these characteristics for the topic under consideration.

² McGarry, M.E.; McColley, S.A. Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on CFTR genotype. *Pediatr. Pulmonol.* 2021, 56, 1496–1503.

Bethesda Office

4550 Montgomery Avenue, Suite 1100N, Bethesda, Maryland 20814
301.951.4422 800.FIGHT.CF Fax: 301.951.6378
www.cff.org email: info@cff.org

Information gathered during scoping may lead us to conclude that further consideration of subpopulations defined by these characteristics is not warranted or that additional information is needed to proceed. In such cases, our scoping document and research protocol will describe our rationale for not including these subpopulations.

The CF Foundation supports ICER's efforts to better evaluate key subpopulations relevant to new therapies. Because CF is a progressive disease, people with CF face increased lung damage as they age. The impact of disease-modifying therapies, such as CFTR modulators, may differ between people with CF who initiate treatment at an early age and those who begin treatment later in life, after already experiencing irreversible lung damage.³ However, as stated previously, in ICER's current proposed framework it is unclear whether identified subpopulations will be based on the demographics of the entire disease population or based on the expectation eligible population for the new therapy. We request additional clarification on how subpopulations will be determined for analyses.

As stated in the current VAF, ICER will consider issuing different evidence ratings for an intervention if there is robust, high-quality evidence that supports substantial differences in the evidence ratings of the intervention across different populations or subgroups.

We caution ICER that a lack of evidence does not constitute less effectiveness, especially given the timing of ICER's reviews near to the initial launch of a new therapy. Often, clinical trials include a study population that will demonstrate the maximum benefit of a treatment. Exclusion from clinical trials does not necessarily indicate that another other population does not experience equally significant clinical benefit. Providing different ratings could impact access if interpreted that a lack of evidence from clinical trials constitutes either a lower rating or no specific mention of the subgroup in the ratings. For example, in CF there was limited inclusion of people with lower lung function, measured by a forced expiratory volume in 1 second (FEV₁) score lower than 40%, in elexacaftor/tezacaftor/ivacaftor clinical trial studies. Despite this, numerous post-approval studies have been published to demonstrate the significant clinical benefits experienced by this population.⁴⁵ We ask ICER to expand on this potential change to describe how it will ensure that they do not inadvertently discount value in populations not studied during the clinical trial process.

Perspective in Economic Models

In each assessment, ICER will continue to report cost-effectiveness results from both the health care system perspective as well as a modified societal perspective. ICER will implement new methods to ensure that cost-effectiveness analyses done according to a modified societal perspective have "non-zero" inputs for impacts on productivity for the patient and caregivers, even when direct data are lacking.

³ Zaher A, ElSaygh J, ElSori D, ElSaygh H, Sanni A. A Review of Trikafta: Triple Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulator Therapy. *Cureus*. 2021 Jul 3;13(7):e16144. doi: 10.7759/cureus.16144. PMID: 34268058; PMCID: PMC8266292.

⁴ Pierre-Regis B et al. Rapid Improvement after Starting Elexacaftor–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and Advanced Pulmonary Disease. *Am J Respir Crit Care Med* Vol 204, Iss 1, pp 64–73, Jul 1, 2021 DOI:10.1164/rccm.202011-4153OCon

⁵ Vincenzo C et al. Effectiveness and safety of elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease with the Phe508del/minimal function genotype. *Respiratory Medicine* Vol 189, 2021, <https://doi.org/10.1016/j.rmed.2021.106646>.

Bethesda Office

4550 Montgomery Avenue, Suite 1100N, Bethesda, Maryland 20814
301.951.4422 800.FIGHT.CF Fax: 301.951.6378
www.cff.org email: info@cff.org

We appreciate ICER's inclusion of non-zero inputs for impacts on productivity, even when direct data is not yet available. As previously stated, the timing of ICER's review may result in limited published evidence for inclusion in the value assessment. Cystic fibrosis is a key example of the importance of including non-zero inputs; anecdotal data through the CF Foundation's Compass case management program has found that more people with CF are interested in returning to pursue education and work due to improved health. This data was not available when modulators were reviewed by ICER in their 2019 assessment and demonstrate how a lack of immediately available evidence may lead to incorrect assumptions on the value of a therapy.

Quantifying Additional Dimensions of Value

No changes are proposed through which additional dimensions of value would receive a quantified weighting in the reference case incremental cost-effectiveness findings.

The Foundation recognizes the need to keep additional dimensions of value as qualitative inputs in ICER's assessments, however we are concerned with ICER's lack of standardized data collection and inclusion of these essential dimensions of value. We urge ICER to standardize how these value inputs are used in their assessments and to include this data in the incremental cost effectiveness findings. By excluding this information, ICER will create a report that is not inclusive of the true impact of new therapies.

Further, we request clarification on how ICER intends to use data such as unmet need and disease severity to support deliberations on the long-term value for money. Given the progressive nature of cystic fibrosis, disease severity is an important consideration in both incremental and long-term value. As is currently written, reductions in lung transplants and delays in disease progression are not adequately included in the incremental cost effectiveness findings, nor is it clear how this data will consistently be given appropriate consideration in deliberations around long term value. Additional details are needed to confirm appropriate, consistent use of this information.

To support tangible consideration of severity as a potential modifier of the value of health gains, we will regularly calculate QALY and evLYG shortfall measures to accompany primary cost-effectiveness analysis results and will include these findings in material presented during public deliberation by appraisal committees on the long-term value for money of treatments.

We appreciate ICER's recognition of the shortfalls of both the QALY and evLYG. The lack of patient relevant information in these models cannot be overstated. Furthermore, the QALY looks solely at longevity. The length of life for a person with CF is determined primarily by the degree and decline of lung disease; therefore, by definition, this endpoint disregards all benefits outside of FEV₁. QALYs cannot adequately inform coverage decisions or value assessments as they exclude patient experience and other benefits outside of lung function, thus severely limiting this model. Highlighting the shortfalls of these models will provide additional recognition that these models are tools to help understand value, and that they cannot be the sole consideration when evaluating the value of a therapy.

Bethesda Office

4550 Montgomery Avenue, Suite 1100N, Bethesda, Maryland 20814
301.951.4422 800.FIGHT.CF Fax: 301.951.6378
www.cff.org email: info@cff.org

Other Changes

ICER will continue to seek opportunities to use real-world evidence within our assessments.

It is essential that ICER continue pursuing ways to include real-world evidence in assessments. We continue to be concerned that the timing of ICER's reviews does not provide sufficient opportunity to collect real-world data to support a lifetime economic model. Without this real-world data, ICER risks severely undervaluing treatments in their model and, while ICER recognizes this limitation, the CF Foundation is concerned that the results of the economic modeling may be incorrectly interpreted or used by payers, the public, and other stakeholders.

Potential Other Benefits and Contextual Considerations

ICER will change the terms used to describe these elements to "Benefits Beyond Health" and "Special Ethical Priorities." The structure of the ICER report will continue to highlight these elements in a separate section.

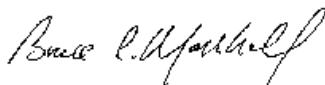
While the Foundation recognizes why ICER separates this section due to the lack of quantifiable data, we have concerns that, by separating these inputs, this data is not given appropriate weight within the report. We urge ICER to consistently incorporate these benefits into the report in a standard way for each review to fully recognize the importance of this data for patient populations.

Patient Engagement Program

We applaud ICER's changes to their patient engagement program to improve patient involvement in the value assessment process. It is essential that members of a disease community can participate in this process as early as possible and that their feedback is heard throughout the entire assessment. We ask that ICER provide diverse opportunities for patient involvement and recognize time and technology limitations that community members may see as barriers to engagement. For example, we encourage ICER to provide opportunities for involvement at a variety of times to accommodate adults and caregivers that are working and unable to join a meeting during business hours.

Thank you for the opportunity to provide feedback on your proposed updates to the Value Assessment Framework. We stand ready to answer any questions you have. Please contact Olivia Dieni, Sr. Specialist, Health Systems Innovation and Navigation, at odieni@cff.org or (240)-200-3715.

Sincerely,



Bruce C. Marshall, MD
Executive Vice President
Chief Medical Officer



Mary Dwight
Senior Vice President
Chief Policy and Advocacy Officer

Bethesda Office

4550 Montgomery Avenue, Suite 1100N, Bethesda, Maryland 20814
301.951.4422 800.FIGHT.CF Fax: 301.951.6378
www.cff.org email: info@cff.org

ICER Value Assessment Framework Updates: Public Comments

2.1 Clinical Trial Diversity

- As socioeconomic status is a determinant of health and individuals with lower socioeconomic status may be disenfranchised from participating in clinical trials, clinical trials may not be representative of the disease population in the US. Therefore, socioeconomic status seems to be conspicuously absent from the consideration of clinical trial diversity. It is acknowledged that socioeconomic status is less commonly collected in clinical trials than the demographic characteristics proposed in the updated Framework. Additionally, paucity of data regarding disease prevalence by socioeconomic status may make the calculation of the representation score difficult for socioeconomic status; however, we believe it is worth including within the Framework and exploring whenever feasible.
- When there are no US disease-specific prevalence estimates available, could ICER please clarify whether additional sources of information would be considered, such as prevalence estimates in a similar disease, alternative (but potentially representative) geographies, or consultation with clinical experts. It would be useful to state in the guidance whether or not there are instances in which a rating would not be calculated.
- We believe that the determination of rating trials conducted exclusively in other countries should be made on a case-by-case basis. Some countries may have a prevalent population that is representative of the prevalent population within the US.

3.1 Perspective in Economic Models

- Within the updated Framework, ICER should provide rationale as to why the same wage rates will be assumed for all patients and informal carers regardless of age, sex, and condition since there are documented differences in wages based on age and sex. These differences should be accounted for in the analysis to ensure these productivity differences are accurately captured.

3.2 Dynamic Pricing Scenario

- We acknowledge the substantial uncertainty inherent in dynamic pricing analysis. However, if ICER considers dynamic pricing for drugs that may be subject to Medicare negotiation, we believe ICER should also consider dynamic pricing for other drugs that may be subject to generic/biosimilar competition to ensure consistency across assessments. This decision could be made on a case-by-case basis but its relevance should be considered.

3.3 Quantifying Additional Dimensions of Value

- We would suggest that ICER use precise language in regard to the statement "we will regularly calculate QALY and evLYG shortfall measures...." Does this mean that shortfall measures will be calculated for every assessment? We would also suggest that ICER specifies whether one of absolute or proportion shortfall will be preferentially considered, both will be considered equally, or if their relevance will be considered on a case-by-case basis.

3.4 Health Benefit Price Benchmarks

- We would suggest that ICER specify how it will be determined whether or not "the comparator therapy price is believed unlikely to meet common cost-effectiveness thresholds." Will this be a quantitative analysis or a qualitative determination? If this is a qualitative determination, we would suggest that ICER include language explaining how these criteria are consistently applied across assessments.

4.1 List of Voting Questions and Voting Format

- We would suggest that ICER define each number on the Likert scale when introducing the voting structure to prevent any misunderstandings.

30 June 2023

Dear ICER value assessment framework committee:

The proposed changes to the ICER value assessment framework are a welcome update, with a great deal of emphasis on important issues such as access to care, equity, and representation in clinical trials. Below are suggestions from Evidera's Evidence Synthesis, Modeling, and Communications Scientific Leadership Council for ICER's consideration. Thank you for the opportunity to provide these comments.

Section 2.2, subpopulation analyses

We applaud the intention to prioritize ethnic and racial diversity in clinical trials, as it is essential for study populations to mirror the real-world patient population in order to properly evaluate efficacy and safety. We believe that ICER could encourage manufacturers to recruit diverse US populations for clinical trials while also acknowledging the value of global clinical data.

If the goal is in part to determine if race-based biological differences impact response to treatment, we would recommend consideration of patient populations outside of the US in the assessment of diversity. For example, Canada, the UK, and several EU nations have increasingly diverse populations, with more uniform access to healthcare than the US, which may lead to more diverse clinical trial enrollment than what is typical in the US.

We recognize that the proposed approach may also seek to capture the specific experience of various racial and ethnic groups living in the US, as social, economic, and cultural factors can impact an individual's experience of health and the healthcare system. This goal is best met by the approach outlined in ICER's proposed changes, to focus on US populations. ICER could consider a framework to acknowledge diverse global trial participants while prioritizing diversity among US patients.

ICER has proposed to use the racial/demographic breakdown of US census data in situations (eg, rare disease) where US patient demographics are not well defined. This approach may cause trials to be assessed as insufficiently diverse simply due to lack of epidemiology data. Rare diseases often have genetic etiologies that may trend in certain ethnic or racial groups rather than following the overall US population breakdown. Likewise, there may be difficulties in applying the proposed scheme to diseases that occur predominantly in one racial group. If the incidence of a particular disease is less than 1.0% in a given racial group, the trial would need to include more than 200 people to avoid being scored as a 0 or 1 for a given racial group. In rare diseases, such an enrollment target would be prohibitive.

Another important component of clinical trial diversity is, as ICER acknowledges, gender diversity. We recommend that ICER explicitly recognize the value of data on transgender and nonbinary individuals in clinical trials and real-world evidence. From a biological perspective, it is important to acquire evidence on whether hormonal therapy or other gender-affirming care may impact the efficacy and safety of treatments for unrelated indications. Such information would support evidence-based healthcare for individuals whose experiences have largely been

omitted from the medical literature. Moreover, gender-nonconforming individuals face numerous challenges in accessing healthcare, and we recommend that ICER's framework support efforts to increase their representation in clinical trials.

Lastly, we would welcome more details on whether the proposed updates to subgroups based on age, gender, and race would impact the cost-effectiveness modeling approach in the value assessment framework. The 2020 framework mentions exploring subgroups in cost effectiveness modeling but is not prescriptive about the approach. Would there be more prescriptive inclusion of these subgroups in the economic analysis in the new framework?

Section 3.4, Health Benefit Price Benchmarks

The consideration of what is an appropriate QALY benchmark acknowledges that in the US, coverage decisions can profoundly impact the patient's own finances. Indeed, taking a cost-effectiveness approach to analyses within the US healthcare system could be considered an invitation to payers to pass greater costs on to patients, leading to greater levels of inequity, financial toxicity, and ultimately poorer health outcomes. Given the potential for willingness to pay for QALY thresholds to increase the cost-sharing burden levied on the patient, we recommend focusing on the higher \$100,000 threshold. Shifting to a \$50,000 threshold is more likely to increase the amount of costs shifted to the patient, rather than to decrease the manufacturer's price. This is apt to lead to situations in which some patients pay out of pocket for non-covered treatments, while others are unable to access the treatment. We recommend explicitly incorporating the reality of financial toxicity into US value assessments.

A2, topic selection; proposed change #1

We would welcome more information on how ICER currently address therapies that require molecular information (eg, molecular diagnostics, next-generation sequencing), in which the treatment may improve disparities but requires testing that is not realistic for underserved populations.

Thank you for your consideration of our comments, and we look forward to seeing the final framework.

Evidera's Evidence Synthesis, Modeling, and Communications Scientific Leadership Council



June 30, 2023

Institute for Clinical and Economic Review (ICER)
14 Beacon Street, Suite 800
Boston, MA 02108

Dear ICER Review Panel:

Genentech appreciates the opportunity to provide input on ICER's proposed changes to the 2023 Value Assessment Framework. As a leading biotechnology company, Genentech discovers, develops, and manufactures novel medicines to treat patients with serious and life-threatening conditions. We remain committed to generating evidence on the clinical, economic and humanistic impacts of our treatments on patients and their families, the healthcare system, and society overall. We believe that discussions of value should involve the full range of healthcare stakeholder perspectives on value to ensure that the right medicines are delivered to the right patients at the right time [1]. Accordingly, we continuously engage with ICER across assessments, framework updates, and policy papers to share recommendations and promote the use of best practices that advance the science of value assessment in the United States.

We commend ICER for many positive proposed updates that better integrate equity considerations in assessment of clinical data, more fully and routinely capture productivity costs in economic models, and improve patient engagement within and across reviews. However, the proposed updates to comparative clinical effectiveness assessment lack adequate consideration of the following: broader regulatory requirements that guide clinical development; updates to long-term cost-effectiveness assessment require changes to meet best practices and align with the current body of evidence on additional elements of value; and planned changes to patient engagement should better support integration of patient insights into economic models. We share our perspectives on ICER's proposed changes below.

SECTION 1: Proposed Changes to Comparative Clinical Effectiveness Assessment

Recommendation 1a: Recognizing the time it takes for manufacturers to implement global health authority recommendations and requirements, ensure that ratings of clinical trial diversity properly consider the timeline for clinical development of new products and the regulatory requirements that impact enrollment. Given that ICER is a US body, we agree that ICER should anchor to a US regulatory framework and US epidemiological and clinical trial

data. However, there is likely to be a lag between FDA guidance on increasing clinical trial diversity and the manifestation of improved representation in trial enrollment. Near-term ICER assessments may be evaluating trials that were designed and recruited before updated FDA guidance was issued, and ICER's ratings and discussion should account for this lag. Further, grounding ICER's proposed clinical trial diversity rating in US epidemiological data is critical, due to likely data limitations and variability of prevalence rates globally. While use of trial enrollment data for US patients by age, sex and race will support a more meaningful assessment of adequate representation, it may not be publicly available. Further, the ability to achieve ICER's thresholds may be impacted by disease rarity, randomization requirements based on regulatory-aligned endpoints, and other factors dictated by global health authorities. These contextual considerations should be summarized and presented alongside numeric ratings to support an appropriate discussion on clinical trial diversity.

Recommendation 1b: Evaluation of clinical evidence on sub-populations should be approached with caution and with consideration of clinical appropriateness, clinical trial design and statistical powering to avoid misinterpretation of treatment effects. The selection of subgroups should be based on established biological and epidemiological evidence [2]. To avoid misinterpretation of treatment effects, ICER should only consider treatment effects in confirmatory subgroups where a plan for control of the type I error and adequate powering for testing of the overall and subgroups treatment effects have been pre-specified in the analysis plan. ICER will have to confirm such with the manufacturer, as these are not usually in the public domain. While ICER's adoption of the ICEMAN tool for confirmatory subgroup considerations is a transparent, standardized and repeatable process, it is not clear how ICER is going to evaluate subgroups given the tool provides a range of ratings from very low credibility to high credibility. We recommend that ICER clarify how the ICEMAN tool will be used to guide their clinical evaluation of subgroups by specifically outlining the ratings (i.e., "high credibility") that would lead to a formal subgroup evaluation and clinical rating.

SECTION 2: Proposed Changes to Long-Term Cost-Effectiveness Assessment

Recommendation 2a: Remove the health improvement distribution index (HIDI) given its flawed approach to capturing critical drivers of health disparities, and instead, utilize distributional cost-effectiveness analysis to better quantify the equity implications of funding and access decisions. Use of the HIDI to frame the vote on health equity will not support an informed discussion on the true drivers of health inequalities and may bias voting for several reasons. First, differences in disease prevalence across race and ethnicity are a poor proxy for the complex geographic factors and social determinants of health that drive health outcomes [3-5]. Second, a measure based on prevalence alone ignores important disparities in access to care, timing of care and appropriateness of care across vulnerable subgroups [6].

Recent data advancements now allow for more routine application of formal equity-informative cost-effectiveness methods, including distributional cost-effectiveness analysis (DCEA), in the US setting [7,8]. These methods offer a standardized way to collect and synthesize information on drivers of health inequalities across the staircase of inequality (as described by Cookson and colleagues), which includes prevalence of disease, timing and variability of access to treatments, subgroup differences in baseline disease risks and treatment effects, and the impact of opportunity costs for resources forgone [9,10]. Integration of this information into a DCEA framework will allow ICER to: (1) inform the expected equity impacts of funding a new treatment; (2) identify and prioritize key data gaps to improve an understanding of existing disparities; and (3) highlight where to plan for policy and public health solutions across the patient journey to best address drivers of disparities. In addition to implementing formal DCEA into ICER's assessment, the information collected on the staircase of inequality should be qualitatively summarized in a section of the report to provide data-driven insights on existing trends and current gaps in evidence across vulnerable population groups [11,12].

Recommendation 2b: ICER should ensure that their indirect approach for estimating productivity costs fully encompasses all relevant time use elements and clearly plans for how to address assessments where limited or incomplete productivity data exist. This important update allows for consistency across ICER's models and will contribute to a more comprehensive understanding of disease burden. Genentech proposes the following revisions to best align with methods outlined in the Jiao and Basu 2023 paper and recommendations of the Second Panel on Cost-Effectiveness [13,14]. First, ICER should account for incremental productivity costs in the baseline period of survival as well as the period of additional survival to ensure productivity gains capture both the impact of life extension but also the impact of delayed disease progression and improved health-related quality of life (HRQoL). Next, we recommend inclusion of costs associated with time spent seeking medical care (e.g., waiting for treatment), which may be impacted by interventions and should be reflected in the societal perspective. Finally, for many assessments, direct productivity data may be available but incomplete, and may therefore underestimate the overall disease and treatment-related impacts to productivity. For example, data may show patient productivity impacts over a limited time period, but ICER would still need to estimate long-term productivity impacts. Until these challenges are adequately addressed through academic discourse, ICER should program the cost-effectiveness model with proxy data and disease-specific data and utilize the option that produces higher productivity costs in the societal base-case.

Recommendation 2c: Include cost-effectiveness scenarios with additional value elements with an accompanying qualitative summary, as evidence on these value elements may influence decision-making for patients, providers and policymakers. Specifically, we recommend that ICER include a cost-effectiveness scenario that includes available evidence on additional dimensions of value informed by ICER's own research and data submitted from key

stakeholders. This scenario should be accompanied by a qualitative summary of additional value evidence that includes commentary from physicians and patient representatives to support informed deliberation of additional dimensions of value. Since publication of the ISPOR value flower, research on more novel elements of value have intensified and begun maturing [15]. These value elements have long played a role in healthcare decision-making implicitly, but now have the opportunity to be explicitly and quantitatively included and deliberated upon [16-20]. For example, methods exist to estimate clinical real option value (ROV) *ex post* and at launch. The growing number of ROV studies illustrate that, in innovation environments where ROV exists, conventional cost-effectiveness analysis (CEA) methods fail to capture between 5-20% of a treatment's clinical value [21-23]. Additionally, real world studies highlight how care shifts in anticipation of new innovations and recently published evidence demonstrates that the majority of clinical oncologists consider ROV in current treatment decision-making [24,25]. While issues of double counting and adjustments to willingness to pay thresholds remain areas of open research in the HEOR community, these issues exist for items that ICER already includes in assessments, such as impacts on productivity and caregivers.

Recommendation 2d: ICER should model multiple cohorts in their dynamic pricing scenario to better reflect the true long-term expenditure for medicines that are likely to undergo drug price negotiation under the Inflation Reduction Act. Genentech recommends a multi-cohort approach with at least 10 years of cohorts for small molecules and 13 years of cohorts for large molecule drugs to appropriately characterize the expected drug expenditures pre- and post-drug price negotiation. ICER's proposed single cohort approach would only track one modeled cohort over the model time horizon, which fails to capture lower drug costs incurred by downstream cohorts, particularly in instances where the intervention of interest is a long-term treatment for a chronic condition or a repeated-dose cure [26]. Published studies examining the impact of dynamic pricing establish the limitations of a conventional single cohort approach in adequately capturing drug lifecycle pricing and recommend the use of a multicohort approach through the time a product is obsolete [26,27].

Recommendation 2e: Ensure that approaches to evolve ICER's willingness to pay threshold (WTP) consider both supply-side and demand-side perspectives, and that integration of additional value elements be considered alongside threshold changes. Regarding the inability to measure related opportunity costs and adjustment of the WTP threshold, this is a recognized challenge across the globe when conducting health technology assessment, as we do not know which health services would be displaced to fund a newly recommended intervention. The WTP literature is varied as to the appropriate perspective and the resulting threshold values both internationally and locally in the US [28-30]. Recognizing this uncertainty, we recommend that both demand-side (societal preferences) and supply-side (health system opportunity costs) perspectives should be considered when evaluating potential changes to ICER's thresholds [31-34]. Further, if ICER proposes to lower their WTP threshold, the value assessment framework should also be updated simultaneously to include additional

elements of value (e.g. value of hope, insurance value and real option value) in the reference case.

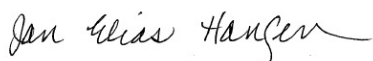
SECTION 3: Proposed Changes to Patient Engagement

Recommendation 3: While ICER proposes several important and meaningful changes to patient engagement, more work is needed to better integrate patient insights into economic models. It is disappointing that proposed updates lack information about how patient-submitted data will impact the process and outcomes of value assessment. Ultimately, if patient input is only considered as a contextual factor and not incorporated into ICER’s economic model, it is not fully valued. To better integrate patient insights into value assessments, we recommend that ICER: (1) implement patient surveys more consistently to fill data gaps and use a range of mixed methods to capture patient input; and (2) provide a 90-day comment period to review all draft evidence reports, as current timelines are not reasonable for meaningful engagement from patient organizations, who often have a small staff and limited resources. Additionally, to provide transparency on the role of patient engagement in ICER’s processes, we recommend ICER release a report detailing progress on the patient engagement plans outlined in the 2020 to 2023 value assessment framework. This report should highlight how ICER worked with patient groups to identify the most important outcomes for patients and include examples of patient-important outcomes that were incorporated into ICER’s economic models to provide clearer guidance on what patient-submitted data has been most impactful.

Conclusion

In conclusion, we applaud ICER for continually refining their value assessment framework and recognize the positive proposed changes that will evolve and improve ICER’s processes overall. We encourage further refinement based on the recommendations above to better support a balanced, evidence-based dialogue on the value of new medicines through robust engagement with a range of healthcare stakeholders and an unwavering adherence to evolving methodological best practices. As an organization that shares ICER’s goal around building a more sustainable healthcare system, we continue to offer our expertise and engagement. Genentech welcomes the opportunity to further discuss how our recommendations can help shape ICER’s iteration and improvement of the value framework for assessments.

Sincerely,



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

Cited References

1. Genentech. It's Time To Rethink Value In Healthcare. Retrieved from: <https://www.gene.com/stories/its-time-to-rethink-value-in-healthcare>. Accessed on: June 22, 2023.
2. Wang X, Piantadosi S, Le-Rademacher J, Mandrekar SJ. Statistical Considerations for Subgroup Analyses. *J Thorac Oncol*. 2021;16(3):375-380.10.1016/j.jtho.2020.12.008
3. Remington PL, Catlin BB, Gennuso KP. The County Health Rankings: rationale and methods. *Popul Health Metr*. 2015;13:11.10.1186/s12963-015-0044-2
4. Bell CN, Owens-Young JL. Self-Rated Health and Structural Racism Indicated by County-Level Racial Inequalities in Socioeconomic Status: The Role of Urban-Rural Classification. *J Urban Health*. 2020;97(1):52-61.10.1007/s11524-019-00389-7
5. Phillips RL, Liaw W, Crampton P, et al. How Other Countries Use Deprivation Indices- And Why The United States Desperately Needs One. *Health Aff (Millwood)*. 2016;35(11):1991-1998.10.1377/hlthaff.2016.0709
6. Gaskin DJ, Roberts ET, Chan KS, McCleary R, Buttorff C, Delarmente BA. No Man is an Island: The Impact of Neighborhood Disadvantage on Mortality. *Int J Environ Res Public Health*. 2019;16(7).10.3390/ijerph16071265
7. Basu A, Schuldt R, Ng C, Sheinson D, Kowal S. MSR60 A Comprehensive View on the Geographic Variation in Racial and Ethnic Disparities in Life Expectancy in the United States. *Value in Health*. 2022;25(7):S529-S530.10.1016/j.jval.2022.04.1267
8. Cookson R, Espinoza M, Kowal S, Carvalho N. Estimating a Country's Social Distribution of Health. Virtual Workshop. ISPOR Europe. Vienna, Austria. November 2022.
9. Cookson R, Griffin S, Norheim OF, Culyer AJ, Chalkidou K. Distributional Cost-Effectiveness Analysis Comes of Age. *Value Health*. 2021;24(1):118-120.10.1016/j.jval.2020.10.001
10. Cookson R, Griffin, S., Norheim, O. F., & Culyer, A. J. *Distributional Cost-Effectiveness Analysis: Quantifying Health Equity Impacts and Trade-Offs*. Oxford: Oxford University Press, 2020. . 2020.
11. Majda T, Kowal S, Corral M. EE459 Racial Health Disparities in Acute Ischemic Stroke: A Targeted Literature Review for Estimates to be Used in Distributional Cost-Effectiveness Analysis. *Value in Health*. 2023;26(6).10.1016/j.jval.2023.03.760
12. Voehler D, Synnott P, Majda T, Ollendorf D, Lin PJ, Kowal S. EE31 Identifying Equity-Relevant Subgroup Effects in Alzheimer's Disease: A Literature Review to Support a Distributional Cost-Effectiveness Analysis. *Value in Health*. 2023;26(6).10.1016/j.jval.2023.03.337
13. Jiao B, Basu A. Associating Health-Related Quality-of-Life Score with Time Uses to Inform Productivity Measures in Cost-Effectiveness Analysis. *Pharmacoeconomics*. 2023.10.1007/s40273-023-01246-x
14. Basu A. Estimating costs and valuations of non-health benefits in cost-effectiveness analysis. In: Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, editors. *Cost-effectiveness in health and medicine*, 2nd edn. Oxford University Press, New York; 2017.
15. 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 Health*. 2018;21(2):131-139.10.1016/j.jval.2017.12.007
16. Khavjou O, Bradley C, D'Angelo S, Buell N, Giombi K, Honeycutt A. PCORI. Landscape Review and Summary of Patient and Stakeholder Perspectives on Value in

Health and Health Care. Retrieved from:

<https://www.pcori.org/sites/default/files/PCORI-Landscape-Review-Summary-Patient-Stakeholder-Perspectives-Value-Health-Care-August-2022.pdf>. Accessed on: June 22, 2023.

17. dosReis S, Butler B, Caicedo J, et al. Stakeholder-Engaged Derivation of Patient-Informed Value Elements. *Patient*. 2020;13(5):611-621.10.1007/s40271-020-00433-8
18. Mudrazija S. Work-Related Opportunity Costs Of Providing Unpaid Family Care In 2013 And 2050. *Health Aff (Millwood)*. 2019;38(6):1003-1010.10.1377/hlthaff.2019.00008
19. Whittington M MR, Kowal S. . Accounting for Equity in Health Technology Assessment. Workshop. ISPOR International. Boston, USA. May 2023.
20. McQueen RB IA, Zemplenyi A, Mendola N, Nemeth B, Kalo Z. Under peer review: Multi-Stakeholder Perceptions of Broader Contextual Value Elements for United States Value Assessment of Health Interventions.
21. Li M, Garrison L, Jr., Lee W, Kowal S, Wong W, Veenstra D. A Pragmatic Guide to Assessing Real Option Value for Medical Technologies. *Value Health*. 2022.10.1016/j.jval.2022.05.014
22. Lee W, Wong WB, Kowal S, Garrison LP, Jr., Veenstra DL, Li M. Modeling the Ex Ante Clinical Real Option Value in an Innovative Therapeutic Area: ALK-Positive Non-Small-Cell Lung Cancer. *Pharmacoeconomics*. 2022;40(6):623-631.10.1007/s40273-022-01147-5
23. Lee W, Li M, Wong WB, To TM, Garrison LP, Veenstra DL. Modeling the Ex Post Real Option Value in Metastatic Melanoma Using Real-World Data. *Value Health*. 2021;24(12):1746-1753.10.1016/j.jval.2021.07.004
24. Li M, Basu A, Bennette CS, Veenstra DL, Garrison LP. Do cancer treatments have option value? Real-world evidence from metastatic melanoma. *Health Econ*. 2019;28(7):855-867.10.1002/hec.3899
25. Li M, Elsis Z, Wong W, Kowal S, Veenstra D, Garrison L. Do future innovations in development influence oncologists' treatment recommendations today? A survey of U.S. oncologists. *Journal of Clinical Oncology*. 2023;41(16_suppl):e24004-e24004.10.1200/JCO.2023.41.16_suppl.e24004
26. Garrison LP, Jr., Jiao B, Dabbous O. Value-Based Pricing for Patent-Protected Medicines Over the Product Life Cycle: Pricing Anomalies in the "Age of Cures" and Their Implications for Dynamic Efficiency. *Value Health*. 2023;26(3):336-343.10.1016/j.jval.2022.09.010
27. Cohen JT. The Impact on Cost-Effectiveness of Accounting for Generic Drug Pricing: Four Case Studies. *Value Health*. 2023;26(3):344-350.10.1016/j.jval.2022.09.011
28. Gloria MAJ, Thavorncharoensap M, Chaikledkaew U, Youngkong S, Thakkinstian A, Culyer AJ. A Systematic Review of Demand-Side Methods of Estimating the Societal Monetary Value of Health Gain. *Value Health*. 2021;24(10):1423-1434.10.1016/j.jval.2021.05.018
29. Iino H, Hashiguchi M, Hori S. Estimating the range of incremental cost-effectiveness thresholds for healthcare based on willingness to pay and GDP per capita: A systematic review. *PLoS One*. 2022;17(4):e0266934.10.1371/journal.pone.0266934
30. The Institute of Health Economics. Theoretical models of the cost-effectiveness threshold, value assessment, and health care system sustainability. Retrieved from: [7](https://www.pmprb-</div><div data-bbox=)

cepmb.gc.ca/CMFiles/Consultations/new_guidelines/IHE_white_paper_for_PMPRB_Final.pdf. Accessed on: June 22, 2023.

31. Phelps CE. A New Method to Determine the Optimal Willingness to Pay in Cost-Effectiveness Analysis. *Value Health*. 2019;22(7):785-791.10.1016/j.jval.2019.03.003
32. Vanness DJ, Lomas J, Ahn H. A Health Opportunity Cost Threshold for Cost-Effectiveness Analysis in the United States. *Ann Intern Med*. 2021;174(1):25-32.10.7326/M20-1392
33. Berdud M, Ferraro J, Towse A. A Bargaining Approach: A Theory on ICER Pricing and Optimal Level of Cost-Effectiveness Threshold. July 2020. Retrieved from: <https://www.ohe.org/publications/bargaining-approach-theory-icer-pricing-and-optimal-level-cost-effectiveness-threshold/>. Accessed on: June 26, 2023.
34. Cubi-Molla P, Errea M, Zhang K, Garau M. Are Cost-Effectiveness Thresholds fit for Purpose for Real-World Decision Making? February 2020. Retrieved from: <https://www.ohe.org/publications/are-cost-effectiveness-thresholds-fit-for-purpose/#post-content>. Accessed on: June 26, 2023.



Global Healthy Living Foundation
515 North Midland Avenue
Upper Nyack, New York 10960 USA
+1 845 348 0400
+1 845 340 0210 fax
www.ghlf.org

June 30, 2023

Submitted by Email

Institute of Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02180

RE: Comments on Value Assessment Framework Proposed Changes 2023

Thank you for the opportunity to provide comments on the *Value Assessment Framework Proposed Changes 2023*. The Global Healthy Living Foundation (GHLF) appreciates the Institute of Clinical and Economic Review's (ICER's) commitment to increasing diversity and inclusion in clinical trials and analysis. However, we remain concerned about ICER's continued reliance on Quality Adjusted Life Years (QALYs) and other health outcome measurements. As highlighted on previous occasion we also want to extend encouragement and support to placing a larger emphasis on real-world evidence (RWE) and exploring new partnerships with organizations to generate this using their own infrastructure.

By way of background, GHLF is a 501(c)(3) non-profit patient group that works to improve the quality of life for people with chronic disease, often focusing on those least able to advocate for themselves. Through our websites, social media channels, and conventional media, GHLF reaches more than 10 million chronically ill people monthly in the United States. GHLF works to improve their quality of life 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 increase the diversity within clinical trials by being more inclusive in terms of age and race, gender and sexuality and disease conditions. We are eager to see how ICER will project the impact of drug pricing negotiations and what it will mean for future drug developments. Additionally, we support ICER's effort to evolve and improve the framework by engaging with patient organizations like ours to develop more transparent, robust and objective models and methods as you develop and define the 2023 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 to ensure it remains objective and does not unfairly favor any one stakeholder group over others. The experience of patients living with a chronic disease is not consistent over a lifetime. There are interruptions and periods of flare, 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 can access treatments, we caution against the use of QALYs alone. As previously stated by us in earlier comments to ICER, QALYs do not adequately reflect the real-world patient experience and remain controversial among many experts. Among other things, QALYs ignore ethical societal concerns and put patients at peril by reducing individuals to an average arbitrary number. The serious problems associated with the QALY measure are 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. Furthermore many chronic diseases do not have static endpoints and hence the use of real world evidence (RWE) and validated measures that capture real world evidence must be integrated into any value assessment framework.

Simply acknowledging the inherent challenges around the QALY while continuing allegiance to similar metrics fails to capture the real world experience of people living with these diseases. . 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 even more reason for ICER to incorporate Real World Data (RWD) and Real World Evidence (RWE) into their model while simultaneously incorporating the patient and caregiver perspectives 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 analysis lies in part on transparency and repeatability. We encourage ICER to provide complete transparency and access to its models. 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 broader multi-stakeholder community.

Respectfully submitted,



Shilpa Venkatachalam, PhD, MPH
Director, Patient-Centered Research Operations and Ethics Oversight
Co-President, GHLF Canada



June 28, 2023

Via E-mail (publiccomments@icer.org)

Steven D. Pearson, M.D., M.Sc. FRCP
President
Institute for Clinical and Economic Review (ICER)
14 Beacon Street, Suite 800
Boston, MA 02108

RE: 2023 Value Assessment Framework Draft Update

Dear Dr. Pearson:

Gilead Sciences, Inc. (Gilead) appreciates the opportunity to submit these comments in response to ICER's draft update to its value assessment framework.

Gilead is a research-based biopharmaceutical company that discovers, develops, and commercializes innovative medicines in areas of unmet medical need. We endeavor to transform and simplify care for people with life-threatening illnesses around the world. Our portfolio of products and pipeline of investigational drugs includes treatments for HIV, liver diseases, cancer, and inflammatory diseases. Gilead is committed to ensuring that people have access to our medicines.

While we support some of the proposed changes, overall we are disappointed that ICER has not done more to address concerns raised previously by Gilead and other stakeholders.¹ These concerns include that ICER's framework and methods are not adequately patient-centered, transparent, aligned with recommended practices, or reflective of the value that innovative medicines bring to patients and society. In this letter, we expand on those concerns and the following points:

- 1) ICER's use of cost-effectiveness to recommend prices is inappropriate, and arbitrary threshold and cost savings adjustments lack scientific basis
- 2) Lack of consideration of societal benefits and additional value elements mean ICER is increasingly out of step with best practices
- 3) Real-world pricing changes over the product life cycle should be fully incorporated into ICER's models
- 4) ICER should be more forward leaning in its approach to patient engagement and health equity, and reconsider its proposals on clinical trial diversity and topic selection
- 5) Real-world evidence (RWE) is critical, but must be used appropriately and transparently

* * * *

1) ICER's use of cost-effectiveness to recommend prices is inappropriate, and arbitrary threshold and cost savings adjustments lack scientific basis

Gilead believes that ICER should discontinue issuing recommended prices, i.e., 'Health Benefit Price Benchmarks.' Because of our multi-payer system and significant differences across patient populations, the U.S. health care landscape is too complex to recommend a single product price based on cost-effectiveness analysis.² Use of flawed cost-effectiveness metrics like the quality-adjusted life

year (QALY) will never provide a precise estimate of a product's value, and may significantly undervalue medicines that treat certain populations.³ Further, many assumptions and uncertainties underly cost-effectiveness analysis, and by extension, the recommended price. However, leading health economists, including ICER's former chief scientific officer, have noted that ICER tends to publicize its recommended prices without reflecting the assumptions and the significant uncertainty of its estimates.⁴

Lowering cost-effectiveness thresholds. Gilead also believes that ICER's assertion that \$50,000 to \$100,000 per QALY or equal value life years gained (evLYG) may be appropriate cost-effectiveness thresholds is highly misguided and not in keeping with consensus in the health economics community. A recent review article found that a threshold of \$100,000 to \$150,000 is the most commonly used range in the U.S. and is "generally consistent with recent theoretical and empirical work."⁵ Moving back towards lower thresholds – especially in a time of significant inflation – would be "moving the goal posts" and would significantly undermine ICER's credibility.

Use of shared savings and cost offset caps. ICER's recent use and new proposals on shared savings and cost offset caps are highly concerning. Use of these adjustments can have dramatic effects on the results of ICER's modeling and its recommended prices. Yet they have no scientific basis, and as ICER has previously acknowledged, the split of shared savings and the amount used for capping cost offsets is completely arbitrary.⁶ For these reasons, use of these adjustments is not in keeping with value-based pricing. They have the potential to significantly undervalue treatments like cell therapy that deliver cures and life-changing improvements to patients' lives, signaling that these treatments are less important to society.

We are also concerned by the lack of transparency related to these changes. ICER suggested that "the field must agree on best practices" for these approaches, but they were initially rolled out in December 2022 and ICER's limited public engagement on this topic occurred nearly 4 years ago.⁷

2) Lack of consideration of societal benefits and additional value elements mean ICER is increasingly out of step with best practices

Gilead has long advocated that value assessment should include the societal perspective as a co-base case and quantitatively include a comprehensive set of value elements. As noted below, use of these approaches is recommended as a best practice by the health economics community. We are disappointed that once again ICER has declined to do so in the draft update.

Use of the societal perspective. The Second Panel on Cost-Effectiveness in Health and Medicine recommended that the societal perspective be employed as a co-base case in cost-effectiveness analyses.⁸ However, in the draft update ICER has once again declined to align with this best practice. We support ICER's intent to use data so that productivity will have "non-zero" inputs, but believe ICER should go much further and expand use of the societal perspective in all assessments.

ICER's refusal to incorporate the societal perspective in previous assessments has been criticized. For example, ICER did not utilize the societal perspective in its assessment of Veklury for the treatment of COVID-19, which was considered by leading health economists to be a "glaring omission" given the significant societal health and economic impacts of the pandemic.⁹ We were pleased to see ICER reverse course in its later assessment of other COVID-19 therapeutics, and hope that the societal perspective will be included as a co-base case in all assessments moving forward.

Quantifying additional value elements. We are concerned that once again ICER is not planning to quantify additional elements of value. The health economics community has identified additional value elements that should be included in value assessment, and methods such as Generalized Risk-Adjusted Cost-Effectiveness (GRACE) demonstrate that such value elements can be quantified and incorporated into analyses.^{10,11} We believe that ICER is clearly incorrect in its blanket statement that consideration of additional elements of value will lead to double counting.

For example, an ISPOR panel recommended that dynamic transmission be taken into account in value assessments in infectious diseases.¹² When an infectious disease like HIV is prevented in one patient, or a patient with HIV has an undetectable viral load, the spread of the virus is reduced and additional cases are averted.¹³ This lack of transmission provides clear health benefits to individuals and society and results in significant avoided health care spending. Methods for including transmission in cost-effectiveness are well developed and have been used for multiple infectious diseases.¹⁴ However, ICER has not done so in previous assessments of antivirals,¹⁵ which means that it may be systematically undervaluing antivirals and other preventive medicines relative to treatments for non-communicable diseases.

Gilead believes that Multi-Criteria Decision Analysis (MCDA) is a more patient-centered approach to value assessment that can facilitate inclusion of a wider array of patient-important value elements. MCDA methods have matured considerably in recent years, and despite ICER's assertion that the method is overly complex, there are examples of it being simplified while still being rigorously applied.¹⁶ We encourage ICER to pilot test a more streamlined version of MCDA to quantify patient perspectives and capture a wider range of value elements.

Consideration of disease severity. We support ICER's additional consideration of disease severity. However, we believe ICER should go a step further and utilize disease severity in a quantitative manner as a modifier, in line with the practice of many other global health technology assessment agencies.¹⁷ This approach aligns with the research consensus that individuals and society place greater value on treatments that address more severe conditions.¹⁸

3) Real-world pricing changes over the product life cycle should be fully incorporated into ICER's models

Gilead believes that ICER's practice of not reflecting pricing changes over a product's lifecycle has resulted in artificially low estimates of cost-effectiveness and Health Benefit Price Benchmarks. We believe that ICER should account for price reductions due to competition, loss of patent exclusivity, and other dynamics. ICER has previously said that the timing of such price changes is too unpredictable to include, but research exists on the typical timing of these price changes.¹⁹

Reflecting the Medicare Maximum Fair Price (MFP). While it is a limited step, we support ICER's proposal to reflect the new Medicare MFP setting process. We believe that the MFP process is highly flawed, but this significant price shock should be included in ICER's modeling. Given the uncertainty of timing of a product's selection for the MFP setting process and the amount of the price reduction, we support ICER using reasonable, general assumptions across product assessments rather than attempting to develop product-specific assumptions. We suggest that when the MFP price reduction assumption is included in an assessment, ICER should discuss these uncertainties as limitations and make clear the adjustment is only an estimate.

However, we believe ICER's assumption that drugs subject to the MFP process will be priced at the ceiling (75% of non-FAMP price) will significantly underestimate the typical price reduction. ICER

should use a more realistic assumption, such as the assumption the Congressional Budget Office (CBO) has used, which is that the typical MFP will be 50% of non-FAMP.²⁰

4) ICER should be more forward leaning in its approach to patient engagement and health equity, and reconsider its proposals on clinical trial diversity and topic selection

Gilead strongly supports the use of more patient- and equity-centered approaches to value assessment; we believe that the patient voices and equity considerations should be at the center of any assessment of the value of a medicine. ICER is taking some important steps in its draft update that we support. However, we believe it can and should go further, including quantifying patient perspectives and piloting emerging equity-focused methods. We also believe that, while well-intended, some of ICER's draft proposals related to equity (e.g., rating clinical trial diversity) should be reconsidered.

Patient engagement program. We are pleased to see ICER's proposals to expand the capture of patient testimonials and engage diverse small groups of patients and caregivers in the scoping phase. The lived experience of patients should meaningfully guide the scoping of any assessment, including the choice of comparators and outcomes used in the assessment.

We were also pleased that ICER for the first time is proposing to compensate patient representatives for their time and contributions. The time and resources required to engage meaningfully in an ICER assessment has long been a barrier for patients and patient advocacy groups, and has prevented many from participating as fully as they would like. Rather than use the amounts listed in the draft update, we encourage ICER to regularly utilize Fair Market Value calculators to determine the appropriate level of payment, such as the tool developed by the National Health Council.^{21,22}

While these steps are needed, we continue to believe that ICER should use methods such as MCDA to systematically capture patients' experiences and preferences and use this information to weight value elements in its assessment. As noted above, MCDA also permits consideration of a broader set of value elements, including equity. A recent white paper from Avalere outlines the importance of MCDA and related patient-centered approaches and tangible steps ICER and other value assessment organizations can take to incorporate them.²³

Rating clinical trial diversity. Gilead shares ICER's interest in improving clinical trial diversity, and we are taking steps to improve the diversity of our clinical trials to align with the demographics of the patient population. These steps include implementing inclusive recruitment and retention strategies that decrease participant burden; identifying and pursuing diverse geographic sites, providers, and investigators; and strengthening our collaborations with patient groups, regulatory agencies, medical professionals, and community organizations.

While we appreciate the goals of a rating system for clinical trial diversity, we believe it is premature to pursue at this time given ongoing policy development. In 2022, the Food and Drug Administration (FDA) released new draft guidance on this topic and a final version is still pending.²⁴ The FDA's recommendations will inform manufacturers' approaches moving forward and should influence any rating system. Additionally, this would be a new topic for ICER and is quite different from its typical work. We suggest that other organizations with experience on the topic lead efforts on a rating system, or at a minimum that ICER work in partnership with such organizations.

Subpopulation analyses. We support ICER's proposal to give additional consideration to appropriate subpopulations in product assessments. This is an important step in addressing health equity; assuming that all patients are the same in their risk, treatment response, and outcomes is a

false assumption that masks health disparities.²⁵ We support the proposal to include an *a priori* list of subpopulations in the scoping document and research protocol. It is essential that manufacturers, patients, clinicians, and other stakeholders have ample opportunity to review proposed subpopulations and provide feedback on the list.

Consideration of equity in topic selection. We believe that health disparities can be an important criterion in selecting topics and medicines for assessment. However, it is incumbent on ICER to consider unintended consequences of this approach. There is a real risk that this will result in disease areas with larger disparities being more likely to be evaluated, and once results are published, payers may further restrict access to patient populations that would most benefit from increased access – exacerbating existing disparities.

More broadly, groups such as the Innovation and Value Initiative (IVI), academic researchers, and others have identified additional steps and are developing new methods to better address health equity in value assessment.²⁶ We support these efforts and as these methods continue to mature, we encourage ICER to consider and potentially pilot them.

5) RWE is critical, but must be used appropriately and transparently


In general, Gilead supports ICER considering RWE in its assessments. RWE may supplement clinical trial evidence and provide additional information on the value a treatment provides, including long-term outcomes and broader value elements. We support ICER considering published RWE studies to inform its assessments.

In-house RWE. However, we have concerns about ICER’s recent practice of generating RWE in-house. In its 2021 reassessment of hereditary angioedema (HAE), ICER analyzed a claims-based dataset and used that analysis to alter an assumption about HAE attacks.²⁷ ICER did not utilize its full process and did not submit this new research for peer-review. In the updated report, ICER noted that “attacks may be underestimated” due to data limitations.²⁸ However, ICER still recommended lower prices for HAE treatments and stated that the treatments were “far less cost-effective than earlier estimates,²⁹” which was reported in the media.³⁰ This use of RWE was not transparent and did not reflect limitations of the analysis or data used. To avoid this in the future, ICER should submit RWE generated in-house for peer-review prior to using in its assessments.

* * * *

Gilead hopes ICER will incorporate these suggestions in its revised framework. If you have any questions, please do not hesitate to contact Russ Montgomery at russ.montgomery@gilead.com.

Sincerely,




Rekha Ramesh
Vice President, Policy
Government Affairs and Policy
Gilead Sciences, Inc.

References

-
- ¹ ICER. “Methods Update: Value Assessment Framework.” January 2020. Available at <https://icer.org/assessment/value-assessment-framework-2020/>.
- ² Cahill, JR. “Traditional Cost-Effectiveness Formulas and Precision Medicines.” *Health Affairs Forefront*, June 1, 2020. Available at <https://www.healthaffairs.org/content/forefront/traditional-cost-effectiveness-formulas-and-precision-medicines>.
- ³ Ibid.
- ⁴ Cohen JT, Olchanski N, Ollendorf DA, Neumann PJ. “The Certainty of Uncertainty in Health Technology Assessment.” *Health Affairs Forefront*, January 26, 2022. Available at <https://www.healthaffairs.org/content/forefront/certainty-uncertainty-health-technology-assessment>.
- ⁵ Neumann PJ, Kim DD. Cost-effectiveness Thresholds Used by Study Authors, 1990-2021. *JAMA*, 2023;329(15):1312-1314.
- ⁶ Chapman RH, Kumar VM, Whittington MD, Pearson SD. Does Cost-Effectiveness Analysis Overvalue Potential Cures? Exploring Alternative Methods for Applying a “Shared Savings” Approach to Cost Offsets. *Value in Health*, 2022; 24(6):839-845.
- ⁷ ICER. “Adapted Value Assessment Methods for High-Impact “Single and Short-Term Therapies” (SSTs) Updated Version.” December 21, 2022 Available at https://icer.org/wp-content/uploads/2022/12/ICER_SST_FinalAdaptations_122122.pdf.
- ⁸ Sanders GD, Neumann PJ, Basu A, Brock DW, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA*, 2016; 316(10):1093-103
- ⁹ Cohen JT, Neumann PJ, Ollendorf DA. “Valuing and Pricing Remdesivir: Should Drug Makers Get Paid for Helping Us Get Back to Work?” *Health Affairs Forefront*, May 2020. Available at <https://www.healthaffairs.org/doi/10.1377/forefront.20200518.966027/full/>.
- ¹⁰ Neumann PJ, Garrison LP, Willke RJ. The History and Future of the “ISPOR Value Flower”: Addressing Limitations of Conventional Cost-Effectiveness Analysis. *Value in Health*, 2022; 25(4):558-565.
- ¹¹ Lakdawalla DN, Phelps CE. “Generalized Risk-Adjusted Cost-Effectiveness (GRACE): Ensuring Patient-Centered Outcomes in Healthcare Decision Making.” *Value & Outcomes Spotlight*. September 2021. Available at [https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-archives/issue/view/patients-versus-process-the-data-and-the-drivers-behind-patient-centered-outcomes/generalized-risk-adjusted-cost-effectiveness-\(grace\)-ensuring-patient-centered-outcomes-in-healthcare-decision-making](https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-archives/issue/view/patients-versus-process-the-data-and-the-drivers-behind-patient-centered-outcomes/generalized-risk-adjusted-cost-effectiveness-(grace)-ensuring-patient-centered-outcomes-in-healthcare-decision-making).
- ¹² Pitman R, Fisman D, Zaric GS, Postma M, et al. Dynamic Transmission Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-5. *Med Decis Making* 2012;32(5):712-21.
- ¹³ National Institute of Allergy and Infectious Diseases. “HIV Undetectable=Untransmittable (U=U), or Treatment as Prevention.” May 2019. Available at <https://www.niaid.nih.gov/diseases-conditions/treatment-prevention>.
- ¹⁴ Chou JW, Baker-Wagner M, Graf M, Heim Z, Mattingly TJ. Incorporating Disease Transmission Dynamics Into Value Assessment. *Health Affairs Forefront*, July 11, 2022. Available at <https://www.healthaffairs.org/content/forefront/incorporating-disease-transmission-dynamics-into-value-assessment>.
- ¹⁵ Ibid.
- ¹⁶ Mendola ND, Oehrlein E, Perfetto EM, Westrich K, McQueen RB. Stakeholder Perception of Pharmaceutical Value: A Multicriteria Decision Analysis Pilot Case Study for Value Assessment in the United States. *J Manag Care Spec Pharm*, 2022;28(10):1190-1196.
- ¹⁷ Office of Health Economics. “NICE’s severity modifier: a step in the right direction, but still a long way to go.” March 2022. Available at <https://www.ohe.org/insight/nices-severity-modifier-step-right-direction-still-long-way-go>.
- ¹⁸ Skedgel C, Henderson N, Towse A, Mott D, Green C. Considering Severity in Health Technology Assessment: Can We Do Better? *Value in Health*, 2022;25(8):1399-1403.
- ¹⁹ IMS Institute for Healthcare Informatics. “Price Declines after Branded Medicines Lose Exclusivity in the U.S.” January 2016. Available at <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf>.

-
- ²⁰ Congressional Budget Office. “How CBO Estimated the Budgetary Impact of Key Prescription Drug Provisions in the 2022 Reconciliation Act.” February 2023. Available at <https://www.cbo.gov/system/files/2023-02/58850-IRA-Drug-Provs.pdf>.
- ²¹ National Health Council. “Value Framework Get-Ready Checklist for Patient Organizations.” September 2016. Available at https://nationalhealthcouncil.org/wp-content/uploads/2019/12/Get_Ready_Checklist.pdf.
- ²² National Health Council. “National Health Council Patient Engagement Fair-Market Value Calculator.” Available at <https://nationalhealthcouncil.org/fair-market-value-calculator/>.
- ²³ Avalere Health. “Infusing the Patient Perspective into Value Assessment.” May 2023. Available at <https://avalere.com/wp-content/uploads/2023/04/Infusing-the-Patient-Perspective-into-Value-Assessment.pdf>.
- ²⁴ U.S. Food and Drug Administration. “Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry.” April 2022. Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations/>
- ²⁵ National Pharmaceutical Council. “The Myth of Average: Why Individual Patient Differences Matter.” January 2022. Available at <https://www.npcnow.org/myth-of-average>.
- ²⁶ The Innovation and Value Initiative. “No Value Without Equity.” March 2023. Available at https://thevalueinitiative.org/wp-content/uploads/2023/03/No-Value-Without-Equity_Synthesis-Insight.pdf.
- ²⁷ ICER. “Observational Real-World Evidence Update. Prophylaxis of Hereditary Angioedema with Takhzyro and C1 Inhibitors: Effectiveness and Value.” August 2021. Available at https://icer.org/wp-content/uploads/2020/10/ICER_Action_RWE_HAE_Report_082421.pdf.
- ²⁸ Ibid.
- ²⁹ ICER. “ICER Uses Observational Real-World Evidence to Update 2018 Assessment on Therapies for Hereditary Angioedema, Finds Therapies Far Less Cost-Effective Than Earlier Estimates.” August 24, 2021. Available at <https://icer.org/news-insights/press-releases/icer-uses-observational-real-world-evidence-to-update-2018-assessment-on-therapies-for-hereditary-angioedema-finds-therapies-far-less-cost-effective-than-earlier-estimates/>.
- ³⁰ Kansteiner, F. “Takeda, CSL hereditary angioedema meds need steep discounts following real-world evidence review, ICER say.” Fierce Pharma, August 24, 2021. Available at <https://www.fiercepharma.com/pharma/takeda-csl-hereditary-angioedema-meds-need-a-steep-discount-following-real-world-evidence>.




ICER Value Assessment Framework

GSK Feedback June 2023

Consolidated feedback from GSK across the categories of clinical trial diversity, long term cost effectiveness and new methods.

1. Clinical trial diversity ratings and other methods adaptations related to health equity.

- GSK would recommend that the framework structure (as described in the ICER [whitepaper](#)) be updated with the upcoming [US OMB race & ethnicity re-categorization effort](#).
- ICER could consider including (or at least accommodate for the inclusion of) Sexual Orientation and Gender Identity (“SOGI”). It is not well adopted across the industry, but is in many discussions and pilot programs, including one at GSK collecting Gender Identity.
- ICER notes that efforts to include CTD in the report will be limited to US-based operations only, and this does not yet seem to be a standard reporting cohort. This may change over time across the industry now with the FDA guidance implementation.
- The impending finalization of the 2022 FDA Guidance for Race & Ethnicity in Clinical Trials will result in a lot of this work being produced by the sponsor organizations. This doesn’t mean that ICER efforts would be unnecessary but seems like this will be duplicative.
- The rating category does not take into considerations people who generally either do not report their race & ethnicity or are from mixed race backgrounds. Recommend a separate demographic category that either scores them separately, or combines Not reported, Mixed race, American Indian Alaska Native and Pacific Islander into its own population. Combining these will provide an ample sample size to categorize them as “Other Race” due to the overall population being much smaller than White, Black, Asian and Hispanic populations.
- The diversity rating doesn’t make sense especially if disease states differentially impact different sub-groups/ages. For primarily a paediatric disease, would there be a penalty for not including 65+? Description of patient diversity is sufficient and users of report can draw their own conclusions on representativeness based on what populations they serve.
- Hispanic and Latino should be maintained as a mutually exclusive population from Race for scoring purposes so that it aligns with standard reporting criteria, or in the future align with [US OMB race & ethnicity re-categorization effort](#).
- The ICER Rating categories should call out representation of patients in Pharma trials from ex-US and US as two separate rating categories. There will be more representation from Black, Hispanic American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander when considering US trial population independently.
- The stated goal of VAF changes focused on quantitative approach to evaluating clinical trail diversity is headed in the right direction, e.g. prevalence estimates using reliable sources for disease -specific prevalence estimates (centers for disease control, Prevention website and Global Burden of Disease database, literature search of peer reviewed journal articles that estimate prevalence of US disease by sex, age, race, ethnicity)\
- Proposed methods could have significant potential for bias. The methods are not achieving equity, they are allowing applicants potentially to achieve good diversity scores by conducting trials in different countries that provide racial diversity without addressing the actual burden of disease. GSK gave a brilliant investor education seminar on this topic this morning using cabotegravir as an example of how to use epidemiological data to guide the appropriate target recruitment for a




ICER Value Assessment Framework

GSK Feedback June 2023

representative clinical trial: ESG Investor Education Event (Clinical Trial Diversity) [Events calendar | GSK](#).

- Their framework isn't requiring applicants to address the disease populations in the US. An applicant could have all White US participants; all the LatinX participants could be from Latin America, Spain, or Portugal; and all of the Black participants could be from South Africa. But if the burden of disease is in Zimbabwe and Senegal, and in the African American population in the US, then the applicant could score well on numbers in racial groups for their diversity score, but would not in any way address equity and actually ensure they are providing clinical trials and access to treatments for the populations who most need the medicines. See below for excerpts from their Proposed Changes, where they are equating diversity with equity. Simple diversity of numbers in a few categories is not the same as equity.
 2. *ICER will provide an overall diversity rating for the following demographic characteristics: race/ethnicity, sex, and age, specifically, adults aged 65 and older. To do this objectively and consistently across all ICER assessments, ICER has developed a framework for evaluating clinical trial diversity based on the potential best practices described in our white paper on Advancing Health Technology Assessment **Methods that Support Health Equity**. Specifically, as shown in Table 1 below, the ICER-developed framework assigns a score that ranges from 0 to 3 to each demographic category based on the estimated participation-to-prevalence ratios. Then, using the cumulative score and pre-defined cut points, a rating of "good," "fair," or "poor" will be used to communicate the demographic diversity of the participants in a clinical trial (see Table 2).*
 3. *In recognition of the potential barriers for multinational clinical trials to reflect the racial and ethnic diversity of the disease population in the US, the racial and ethnic diversity rating will focus only on the subgroup of patients recruited exclusively in the US if these data are available; if these data are not published and not provided to ICER, ICER will focus on the diversity of the entire trial population. Trials conducted exclusively in other countries will not be rated on race and ethnicity, as they are unlikely to be representative of the racial and ethnic diversity of the US population.*
- ICER's White Paper on Health Equity was published before GSK published the article on Demographic Diversity of US Based Participants in GSK sponsored interventional clinical trials. ICER should consider input from this paper to ensure that as they move to scoring clinical trial diversity, ICER considers using Benchmarking in line with epidemiologic data will allow them to better assess trial enrolment goals, with the aim of evaluating more demographically balanced, diverse, and representative clinical trials and enabling a better understanding of drug safety and efficacy per demographic group.




ICER Value Assessment Framework

GSK Feedback June 2023

- Recommend that ICER strengthen language regarding the following on page 21 of the White Paper, **“Even if clinical evidence suggests differences in the magnitude of net benefit by race, ethnicity, or socioeconomic status, do not calculate cost-effectiveness estimates for subpopulations defined solely by these characteristics.”** There are many reasons why subpopulation data may not show the same net benefit of the overall clinical trial; e.g., GSK’s EMBRACE Study for Benlysta in African-Americans did not meet it’s primary endpoint. ICER needs to strengthen their language so that organizations do not conduct cost-effectiveness analysis on these subpopulations when net benefit is not shown to avoid expanding current or future health disparities. For example, if African-American women showed less clinical benefit to pain meds during pregnancy doesn’t mean they should not receive pain meds during pregnancy.

- 2. Cost-effectiveness scenarios related to potential effects of Medicare drug price negotiation.**
 - ICER will consider the CMS negotiated price (maximum fair price) as one data point or factor when conducting assessments for products (either in the class or new entrants). Based on CMS’ draft guidance, GSK are not confident that CMS will provide a price that reflects the holistic value of a product. CMS’ methodology will rely on therapeutic alternatives as the starting point for price and then adjust based on clinical factors (unmet need etc) as well as manufacturer data (R&D recoupment, unit cost, etc.). GSK view is that the negotiated price will likely be on the lower end. If this lower price feeds into ICER assessments, it will further drive down ICER’s suggested cost effectiveness / pricing.
 - Within the “perspective for economic models” section, impacts may be more than productivity. Concerns with CEA in general still stand for US market that is not a single payer system.
 - Within the “dynamic pricing scenario” sections, consider if the assumption is fair for all drugs. Not all drugs would make it onto the list for price renegotiation.
 - Within the “quantifying additional dimensions of value” section, consider how the methodological issues will be weighted.

- 3. New methods to ensure that cost-effectiveness analyses done according to a modified societal perspective have “non-zero” inputs for impacts on productivity for the patient and caregivers, even when direct data are lacking.**
 - We applaud ICER for taking the step to be more inclusive and include value elements beyond direct costs, and improvement in life expectancy and quality of life, such as patient and caregiver productivity. Especially, taking this step when methods to estimate such impact are still evolving and not perfect. We would like to clarify on this change and provide our suggestions:
 - We kindly request that the ICER (Institute for Clinical and Economic Review) provide clarification regarding the criteria for incorporating productivity costs into the modified societal perspective analysis. In our opinion, it is essential to include



ICER Value Assessment Framework

GSK Feedback June 2023

productivity costs for both patients and caregivers in all assessments, conducting a modified societal analysis as the default approach. This recommendation is based on the understanding that various conditions and targeted interventions are likely to have a certain degree of impact on patients' quality of life. By employing the methodology outlined by Jiao et al. (Jiao and Basu 2023), this impact can be quantified in monetary terms. Adopting such an approach would eliminate the need for a subjective assessment of whether including productivity costs is justified or not, allowing the results from the modified societal analysis to inform whether it should be presented alongside the reference case analysis.

- The current language implies that productivity costs will be considered solely for the periods of life extension. However, we highly recommend, as emphasized and suggested by Jiao et al. (Jiao, B. and A. Basu (2023). "Associating Health-Related Quality-of-Life Score with Time Uses to Inform Productivity Measures in Cost-Effectiveness Analysis." Pharmacoeconomics), that productivity implications be included for both health improvement and extension of survival. As the authors aptly state, 'Economic evaluations that overlook the impact on morbidity may inadvertently favor interventions that solely provide survival gains without functional benefits’.
- With respect to the suggestion to discuss lowering the health benefit price benchmark threshold in the future, ICER should consider pre-empting the threat as a lot of extensive work will be required to identify the true opportunity cost and, as it happened in the UK, it is unlikely to take us anywhere to robustly set a new threshold. On the matter, Culyer’s et al paper from 2007 still stand. Also, the suggestion of using a threshold based on opportunity cost depends on the application of a ‘extra-welfarist’ approach, which most would argue could not apply to the US and certainly should not be considered if a societal perspective is of relevance.
- Regarding proposals for ‘other changes’, ICER should consider the long-term benefit of innovation and the possibility to capture the post-patent benefit into the value of market introduction since there may be an opportunity there to bring the discussion of capturing long-term innovation to the forefront



The professional society for health economics and outcomes research

Improving healthcare decisions

505 LAWRENCE SQUARE BLVD SOUTH
LAWRENCEVILLE, NJ 08648

P +1-609-586-4981
F +1-609-586-4982

info@ispor.org
www.ispor.org

**2022–2023
Board of Directors**

June 30, 2023

President

Jan Elias Hansen, PhD
Genentech
San Francisco, CA,
USA

President-Elect

Brian O'Rourke, PharmD
Brian O'Rourke
Healthcare Consulting
Ottawa, ON, Canada

Past President

Isao Kamae, DrPH, MD
University of Tokyo
Tokyo, Japan

Directors

Eberechukwu
Onukwugha, PhD
University of Maryland
Baltimore, MD, USA

Lotte Steuten, MPhil, PhD
Office of Health Economics
London, England, UK

David Thompson, PhD
Open Health Evidence &
Access
Boston, MA, USA

Beth Devine, PhD
University of Washington
Seattle, WA, USA

Marlene Gyldmark, MPhil
Roche Diabetes Care
Basel, Switzerland

Andrea Manca, MSc, PhD
University of York
York, England, UK

Dong-Churl Suh, PhD
Chung-Ang University
Seoul, South Korea

Treasurer (2020-2023)

Sean D. Sullivan, BSc,
Pharm, MSc, PhD
University of Washington
Seattle, WA, USA

CEO & Executive Director

Rob Abbott
ISPOR
Lawrenceville, NJ, USA

Dear ICER:

ISPOR – the professional society for health economics and outcomes research (HEOR) - is pleased to respond on behalf of its membership to your consultation entitled “2023 Value Assessment Framework - Proposed Changes.”

ISPOR is a scientific and educational society with many of its members engaged in evaluating health technologies, including pharmaceuticals, medical devices, and other interventions. We have a large membership living and working in 110 countries globally, across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government, and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

The response to this consultation was led by the Policy Outlook Committee of our most senior advisory body, the Health Science Policy Council. To engage our membership, we consulted with interested members of Institutional Council (ie, industry and consulting), the 2023 ISPOR Health Technology Assessment Roundtable – North America, and our Real-World Evidence, Health Equity in Research, Rare Disease, and Patient Centered Special Interest Groups, as well as soliciting our general membership for comments. The attached document provides both summary and line-by-line responses based on their comments. We hope they prove useful.

ISPOR would be happy to answer any questions about our response, and to participate in any follow-up consultations on the relevant program items mentioned within the report.

Sincerely,

Robert Abbott
CEO & Executive Director
ISPOR

“ICER 2023 Value Assessment Framework - Proposed Changes”

General comments

We applaud ICER on its efforts to regularly update its value assessment framework based on emergent scientific and societal considerations as well as stakeholder input. The proposed changes address several areas in which there have been recent developments that merit explicit treatment in the framework. Unfortunately, the public comment period was too brief to allow for us to solicit and curate a robust set of comments from ISPOR members, so we provide some brief comments below which we hope will be helpful.

Comments by section

2.1 Clinical Trial Diversity

We agree that it is helpful to encourage and measure clinical trial diversity, as well as to pay closer attention to the US subgroup of global trials. The “representation score” approach per se seems novel and potentially fit-for-purpose though it will take some time to test and ascertain its utility. It should be recognized that as a “nudge” for sponsors to ensure diversity in trial populations, albeit not the only voice in this area, it may take some time for it to take effect given that many trials that will support drug approvals in the near future are already complete or nearly so.

2.2 Subpopulation Analyses

We also encourage attention to subpopulation analysis, both for the designated demographic groups and for other subpopulations viewed as relevant to the specific treatment, as long as there is due attention to statistical and other evidence considerations. We find it interesting that you choose not to estimate cost-effectiveness by subgroup when such differences are found, however. Certainly, any such differences should not drive pricing that discriminates across subgroups. However, heterogeneity of treatment effect is most often driven by baseline risk differences¹, and marginalized and other vulnerable patient groups often have higher baseline risk. Thus, finding that treatment is more cost-effective in such groups could allow for more proactive approaches with them for treatment awareness and access. We understand reluctance to accept a situation in which evidence suggests a disadvantaged group may get less treatment benefit. However, a nuanced and flexible approach can be adopted if equity is viewed as important.

3. Long term cost effectiveness

3.1. Perspective in Economic Models

Productivity costs for both patient and carer are legitimate and important aspects of a societal perspective in cost-effectiveness analysis (CEA), and we support their inclusion in ICER’s calculations. The recent work of Jiao and Basu² provides a useful approach to calculating productivity costs for patients when health related quality of life (HRQoL) data are available but productivity data per se are not, and a lower value for lost leisure consumption time seems justified. Further thought may be needed regarding estimation/modelling of long-term productivity costs given the many factors and incentives involved.

3.2 Dynamic Pricing

¹ Kent, D.M., J. Nelson, I.J. Dahabreh, P.M. Rothwell, D.G. Altman, and R.A. Hayward. 2016. Risk and treatment effects heterogeneity: re-analysis of individual participant data from 32 large clinical trials. *International Journal of Epidemiology* 45(6): 2075-2088.

² Jiao B, Basu A. Associating Health-Related Quality-of-Life Score with Time Uses to Inform Productivity Measures in Cost-Effectiveness Analysis. *PharmacoEconomics*. 2023 Mar 6:1-3.

We appreciate that ICER recognizes that conventional CEA, when used to justify a launch price, has generally ignored the fact that patented medicines eventually go off patent and the compound is usually subject to generic or biosimilar competition. We would argue that our field and ICER should make a concerted effort to model this more accurately. Plausible transitions to generic/biosimilar competition could be modeled. Arguably, modeling could consider how value and price might be affected during the patent protection period were follow-on compound to enter and compete. At this point that should be a cited limitation of the proposed updated framework.

ICER's plan to only do "dynamic pricing" for only the Medicare-eligible population is too narrow. Assuming that manufacturer would receive the IRA "ceiling price" seems unrealistic given the power of CMS in the negotiation. A plausible range should be used.

More generally, our field and ICER needs to begin to explore the impact of considering the value generated for the entire population over entire product life cycle. A recent themed section (March 2023) in *Value in Health* illustrates this perspective and provides numerical examples and estimates.

3.3. Additional Elements of Value

We appreciate the recognition that ICER has given to the work of the ISPOR Special Task Force (STF) on US Value Frameworks that led to the ISPOR Value Flower and the STF recommendation that, for purposes of health technology assessment and formulary inclusion, we need to move beyond conventional CEA to consider other elements of value related to uncertainty and to broader societal impacts.

To this end, we welcome the proposal to include productivity effects, as we comment in section 3.1 above. We also welcomed the inclusion of an interpretation of the "value of hope" in the 2020 ICER Methods Guide. We note and welcome the proposals to use absolute and proportional shortfall measures to help provide a qualitative estimate of disease severity. This is a helpful step towards potentially including a quantitative severity adjustment. We recognize concerns over any potential double counting of benefits or lack of consideration of opportunity cost. We would argue, however, that generalized risk-adjusted CEA (GRACE) calculations could also be considered. Our field has made significant progress in the last five years in moving this "augmented CEA", as it was called by the STF, forward. In particular, the work of Darius Lakdawalla and Chuck Phelps on GRACE^{3,4,5,6} has advanced to the point that it can be estimated, using a number of assumptions, at the very least in a way that can provide an alternative scenario analysis for qualitative consideration in ICER assessments.

One important implication of the GRACE framework is that there would be, in effect, a variable cost-effectiveness threshold that depends on the severity of the underlying condition (or disability level) of the patient. For some conditions, the cost-effectiveness (CE) threshold could be below the \$100K threshold that

³ Lakdawalla DN, Phelps CE "Health Technology Assessment with Risk-Aversion in Health," Journal of Health Economics, July, 2020, 102346.

⁴ Lakdawalla. DN and Phelps, CE. "Health Technology Assessment with Diminishing Returns to Health: The Generalized Risk- Adjusted Cost-Effectiveness (GRACE) Approach, Value in Health 2021; 24(2): 1244-249

⁵ Lakdawalla DN, Phelps CE "A Guide to Extending and Implementing Generalized Risk-Adjusted Cost-Effectiveness. (GRACE)", European Journal of Health Economics, Sept 8, 2021.

<https://doi.org/10.1007/s10198-021-01367-0>.

⁶ Lakdawalla DN, CE Phelps. "The Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Model for Measuring the Value of Gains in Health: An Exact Formulation," Journal of Benefit-Cost Analysis, 2023 14(1):1-24.

ICER uses, and for others, particularly rare conditions, it could be much higher. As we noted above, there is still work to be done to deal with concerns about double-counting, but these issues are being addressed in a way that means we can move forward, at least in a qualitative sense. In addition, the (incremental) value of health risk protection—ie, the peace of mind that a health plan member can get from knowing that something can be done about a condition were they to get it—can provide substantial value that is not reflected in conventional CEA and should be given consideration by ICER.

3.4 Health Benefit Price Benchmarks

We agree that ICER should use a range of alternative cost-effectiveness thresholds to illustrate the potential range of prices that ICER's assessment of clinical value would support. US has heterogeneous plans with very different opportunity costs, and it makes sense, at a minimum, to keep the use of \$100K and \$150K. We note, however, that the paper quoted that concludes with an estimate of an opportunity cost of \$104K is intended to be an estimate of the marginal health impact on those on low incomes having to drop or reduce insurance coverage in response to premium increases. It is not obvious to us how this estimate can be used to support use of a \$50K threshold. We note also the use of a much higher figure than \$150K by the Congressional Budget Office (CBO) when reviewing the potential impact of drug price negotiations as proposed in the Elijah E. Cummings Lower Drug Costs Now Act.⁷ It seems to us that a number of alternative additional thresholds above and below the current ICER illustrative figures of \$150K and \$100K could be relevant and should be considered.

On shared savings analysis we agree it is useful to continue. Arguably the conceptually correct approach is to price the comparator at a price at which it is cost-effective, although we recognize that this may reduce the incentive for companies to develop drugs that will save health systems money. The proposed alternatives (1b i. and ii.) on page 14 therefore make sense.

We would also argue that neither the HEOR field nor ICER have adequately addressed the issue of how the CE threshold from a societal perspective would differ from that for the healthcare perspective. Until this is addressed, it will be difficult for users of ICER's analyses to factor this into their decision making.

3.5 Other changes

We encourage the use of real-world evidence (RWE) in all its various facets in ICER reviews – external control arms for comparisons, baseline costs and risks, other modelling parameters, generalizability to real-world populations and subpopulations, etc.

4. Voting

Just one minor comment, given the short time frame. In point 2, when you consider “average” Likert scores, we suggest you consider both mean and median scores (you may already be doing so), given that strategic voting can skew mean scores. In general, we support ICER's pragmatic approach to voting approaches and its willingness to evaluate how well particular arrangements have worked. We realise this is difficult. However, we would appreciate a longer input period to give more considered feedback.

A.2

We agree that there is merit to having clear mechanisms for integrating health equity considerations into topic selection.

⁷ Congressional Budget Office, 2021. : <https://www.cbo.gov/system/files/2021-02/56905-Drug-Price-Negotiations.pdf>

A.3 Stakeholder engagement

Getting patients onboard is essential, so this process is pivotal. Yet doing this through an online form may not be adequate. A qualitative approach like semi-structured interviews or focus groups should also be considered to engage with patients, caregivers, the general public, and possibly from industry as well. Also consider the framework for patient engagement proposed by Mullins et al.⁸

We would like to acknowledge ISPOR members Lou Garrison and Adrian Towse for their assistance in assembling these comments, as well as ISPOR staff Richard Willke and Kelly Lenahan.

⁸ Mullins CD, Abdulhalim AM, Lavalley DC. Continuous Patient Engagement in Comparative Effectiveness Research. *JAMA*. 2012;307(15):1587–1588. doi:10.1001/jama.2012.442

June 30, 2023

Steven D. Pearson, MD, MSc
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108
Email: publiccomments@icer.org

RE: Public Comments ICER's 2023 Value Assessment Framework: Proposed Changes

Dear Dr. Pearson:

Thank you for the opportunity for the Innovation and Value Initiative (IVI) to comment on your proposed changes to the ICER Value Assessment Framework. IVI is a 501(c)3, non-profit research organization committed to advancing the science, practice, and use of patient-centered health technology assessment to support decisions that make healthcare more meaningful and equitable.

IVI's comments to ICER can be summarized as falling under three major themes:

- Aspects of true patient engagement are still missing from the framework. Full partnership with patients and patient organizations is a necessity going forward. Patients should be included as co-leaders and true partners throughout the HTA process (from before topic selection to final recommendations).
- More information, both in quantity and substance, is needed regarding health equity and its incorporation into the revised framework. Beyond initial inclusion, we urge continuous improvement in how health equity measures are included in HTA processes, data, and methods (i.e., no static solutions will suffice).
- There is a need for more explicit processes for formal incorporation of non-traditional data (e.g., qualitative lived experience and mixed methods) as well as formal processes for what to do when quantitative data are missing (i.e., emphasize gaps rather than "building models to the data").

1. Introduction

In revising its value assessment framework, IVI recommends that ICER consider the comments below related to proposed methodological changes, patient engagement strategies, and methods for handling data gaps.

1.1. Overarching Purpose and Principles of the ICER Value Assessment Framework

We appreciate that ICER is incorporating metrics from its recently published white paper, "Advancing Health Technology Assessment Methods that Support Health Equity," into its proposed revised value framework. But we encourage further incorporation of patient engagement, data diversity, and mixed method approaches to ensure the cultivation of health equity within HTA. In addition, we encourage ICER to continue advancing and incorporating research to make health equity an integral part of HTA methodology and the entire HTA process.

1.2. Population Perspective and Intended Uses of the ICER Value Assessment Framework

ICER should ensure that patient representatives are fully included as co-leaders throughout the HTA process, including in decision-making and scoping, analytic and reporting decisions, and final recommendations. This patient involvement should be representative of the diversity of underlying disease populations, and should include patients from groups that may not be adequately represented in clinical trials or other available data. Effort should also be made to include patients with lived experience beyond those who are formally affiliated with patient advocacy organizations, to help ensure diversity of opinion.

ICER should continue to expand and deepen the ways in which it engages patients with lived experience and patient advocacy groups in the HTA process. For true engagement, ICER should incorporate more patients as equals on HTA evaluation teams, by including them in decision-making from the selection and scoping of topics to the conduct of analyses and reporting of results, not just in advisory positions.

2. Comparative Clinical Effectiveness

2.1 Clinical Trial Diversity

We commend ICER for its plan to evaluate the diversity of participants in clinical trials. However, it is unclear exactly how these changes will be reflected in ICER's reports and recommendations. It would be useful if ICER would explicitly commit to specific reporting requirements and formats for inclusion of these equity-related factors. It is not yet clear how ICER's diversity ratings will be weighted in or incorporated into overall assessments. Additional transparency into how ICER's diversity ratings will be incorporated into overall assessments would be helpful. ICER should explicitly clarify how the diversity rating will be used in ICER's reports and by its voting panels.

We would also encourage ICER to follow and align its actions with efforts that the US Food and Drug Administration (FDA) already has begun in this area, to avoid redundancies or misaligned recommendations. In addition, while race/ethnicity, sex, and age are important dimensions to consider in health equity, it is also important to use a data-driven approach to uncover subgroups that have worse outcomes that we might not necessarily know of *a priori*. Engagement with patients and stakeholders can shed light on this.

2.2 Subpopulation Analyses

While ICER will consider issuing different evidence ratings for a single intervention if robust, high-quality evidence supports substantial differences in the evidence ratings of the intervention across different populations or subgroups, it would be helpful to have more explicit details on how evidence ratings will be handled when evidence across subgroups is inconclusive, mixed, or missing. In addition, ICER should consider analyses that measure the opportunity to reduce health disparities across subpopulations affected by the disease and treatments being evaluated.

3. Long-Term Cost Effectiveness

3.1 Perspective in Economic Models

ICER should consider following the recommendations of the Second Panel on Cost Effectiveness in Health and Medicine¹ to include societal perspective as part of its base case analyses in all assessments.

We commend ICER’s plan to include “non-zero” inputs for impacts on productivity. In addition, ICER’s assessments should strive to calculate a broader definition of economic burdens and financial impacts on patients, beyond direct and indirect medical costs. IVI’s recently published Economic Impacts framework² can provide guidance on how to systematically catalog and consider these costs in a comprehensive manner.

3.2 Dynamic Pricing Scenario

IVI encourages the use of dynamic pricing scenarios for all assessments, not just those “predominantly targeted to Medicare-eligible populations.” The current approach does not account for the fact that generic entry may occur for non-Medicare targeted drugs, making them likely to be much cheaper over time. We also encourage ICER to revisit its assumptions around likely price reductions as the relevant IRA provisions are implemented, to ensure they reflect the policies actually implemented.

The proposed dynamic pricing modeling also focuses on one cohort of patients. The societal benefits of novel health technologies may also benefit many future generations, who would be able to enjoy the technologies at a much lower price.

3.3 Quantifying Additional Dimensions of Value

We commend the use of shortfalls to consider severity. We would also encourage ICER to explore the use of GRACE-type analyses, as a framework that allows for consideration of risk aversion and disease severity. We also believe that more attention should be given to quantification of caregiver burden, as the impact of this may be larger than expected in many cases.

More details around the use of the Health Improvement Distribution Index (HIDI) would be helpful. It is unclear what the implications of using the HIDI will be, and how it will be incorporated into the deliberative process (e.g., does this imply that we will allow for a higher price for treatments because of the potential to lower disparities?). Also, the HIDI may be helpful to decision-makers, but it does not sufficiently capture what needs to be considered to incorporate health equity in HTA. While this index may be considered a good starting point, considering only prevalence is not enough, so we encourage ICER to continue exploring additional equity-related metrics.³

We also point out that the opportunity cost-based approach to estimate cost-effectiveness thresholds is subject to important limitations in methodology and data (see Sampson 2022⁴ for a

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. doi:10.1001/jama.2016.12195

²https://thevalueinitiative.org/wp-content/uploads/2023/06/05-2023-Economic-Impacts-Framework-Report_FINAL.pdf

³ https://thevalueinitiative.org/wp-content/uploads/2023/03/No-Value-Without-Equity_Synthesis-Insight.pdf

⁴ Sampson C, Zamora B, Watson S, et al. Supply-side cost-effectiveness thresholds: Questions for evidence-based policy. *Applied Health Economics and Health Policy* 2022;20(5):651–667.

detailed examination of these limitations). Having one threshold for all disease states and all subpopulations may also ignore heterogeneity across populations and might risk worsening equity and efficiency trade-offs (Hernandez-Villafuerte 2022⁵). This is even more of a concern in a system like the US with multiple payer types with different opportunity costs.

Lack of a clear cost-effectiveness threshold in these cases should not completely block off the consideration of additional value elements. As pointed out by the framework document, cost-effectiveness is just one of many factors to be considered in a deliberative process for HTA. All these point to the need for development of deliberative methods that consider all these factors.

Mixed methods, including quantitative and qualitative analyses, should be considered as part of deliberative processes used in HTA by learning from methods used in other research areas. For example, ICER should continue to test and operationalize methods such as MCDA that will allow consideration of a broader set of value elements that matter to society. How assessors weigh these additional value elements beyond traditional CEA is an important area for exploration.

We would also like to emphasize that analysts cannot wait for perfect data to incorporate certain elements of value. Rather, it may be necessary to develop scenario analyses that explore changes to results using plausible assumptions for missing data. This can show where the provision of missing data has the potential to change decisions (or not), and to guide further research into missing data.

3.4 Health Benefit Price Benchmarks

To further allay concerns about the quality-adjusted life year (QALY), ICER should consider the use of alternative measures beyond equal value life-years gained (evLYG), such as Health Years in Total (HYT). Please also see our comments above regarding the opportunity cost perspective for determining cost-effectiveness thresholds.

The specific scenario analyses for SSTs seem arbitrary, so ICER should consider providing a range of scenario analyses that use different shared saving proportions or cost offsets, and more explicit guidance on when these will be applied to the Health Benefit Price Benchmarks (HBPB)

3.5 Other Changes

In updating assessments with RWE, accountability for equity-related data collection and incorporating this data into assessments is a necessity. We strongly encourage ICER to consider sensitivity or scenario analyses using plausible ranges when preferred data are not available.

4. Potential Other Benefits or Disadvantages and Contextual Considerations

4.1 List of Voting Questions and Voting Format

ICER should more explicitly discuss how its assessments will consider the socioeconomic impacts of new health technologies. How will such impacts be measured and reported, and how

⁵ Hernandez-Villafuerte K, Zamora B, Feng Y, Parkin D, Devlin N, Towse A. (2022). Estimating health system opportunity costs: The role of non-linearities and inefficiency. *Cost Effectiveness and Resource Allocation* 2022;20(1):1-13.

are ICER's voting panels expected to account for these? Will panels be given explicit, detailed instructions for how to consider these issues or will this be more subjective?

In addition, ICER's panel voting and report recommendations should be worded to more explicitly ensure that their recommendations are not construed to unintentionally reduce access to care for patients.

ICER Processes for Conducting Value Assessments

A2. Topic Selection

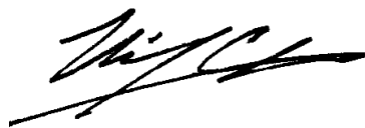
ICER should ensure that patient representatives are fully included as co-leaders throughout the HTA process, including them in the topic selection and scoping processes. Patient engagement should begin as early in the HTA process as possible, before the point of deciding the disease area and topic selection, and before scoping.

A3. Stakeholder Engagement

We commend ICER's efforts to enhance their patient engagement processes, and their commitment to ensure patients' time and contributions to assessments are fairly compensated. As those most directly affected, patients and patient groups should especially be involved in the HTA process. For true and valid engagement, HTA programs must incorporate patients as equals on HTA evaluation teams by including them in decision-making, including the selection and scoping of topics, not just in advisory positions. An inclusive, transparent, and participatory process with a large and diverse set of stakeholders, especially those with lived experience, should be used throughout the HTA process, to ensure multiple, meaningful opportunities for feedback. Importantly, ICER's reports, and other publications should note how patient and other stakeholder input guided and changed the assessment process.

For "Share Your Story," ICER should consider that using an online form to collect patient input might not capture subgroups with challenges in accessing the internet. It would be helpful to have more explicit mention of ways in which ICER will try to identify and recruit under-represented subgroups for this.

We appreciate the opportunity to provide input to ICER's 2023 Value Assessment Framework: Proposed Changes. Please do not hesitate to contact me for further discussion.



Rick Chapman, PhD
Chief Science Officer
Rick.Chapman@thevalueinitiative.org
Innovation and Value Initiative

June 30, 2023

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

Delivered electronically: publiccomments@icer.org

Dear Dr. Pearson:

Merck & Co., Inc. appreciates the opportunity to provide comments on the proposed updates to the ICER Value Assessment Framework. We share ICER's interest in ensuring American patients have access to high value health care and appreciate ICER's attempt to evolve its value framework to meet the demands of stakeholders across the health care ecosystem. Our comments offer recommendations on ICER's proposed changes as well as areas of the existing framework that ICER is not planning to update but warrant attention. We hope that ICER thoughtfully considers and incorporates our recommendations to ensure it delivers on its intention to provide transparent, unbiased, patient-centered evidence aligned with scientific best practices.

Comments on proposed changes to the value framework:

1. Quantifying Additional Dimensions of Value: evLY/QALY shortfalls

ICER has begun to incorporate and promote a calculation of equal value of life-years gained (evLYG) more prominently into its reports. The evLYG values all gains in life-years at the full value of a healthy life-year, such that regardless of age, disability, or illness, all life-year gains are valued equally. In general, treatments with greater life extension and where the quality of life (QoL) of surviving patients is low will see the greatest potential benefit from the evLYG metric compared with the QALY metric. This would potentially include certain treatments for cancer (particularly those affecting younger patients) and gene therapies for debilitating, deadly diseases, while diseases where treatments only, or primarily, improve QOL (e.g., migraine, depression among cancer patients) will see minimal or no benefit. Thus, using evLYG shortfall may not reflect the true unmet need for all conditions.

We encourage ICER to be more patient-centric by asking patients directly how they value their life expectancy (LE)/QoL for a disease condition. Patients with low LE/QoL will value gains in LE/QoL more than patients with greater LE/QoL. Therefore, ICER should adopt Generalized Risk Adjusted Cost-Effectiveness (GRACE) methods to account for patient preference patterns that will lead to diminishing returns. GRACE accounts for the concept that the value of extending life years should similarly account for the greater relative willingness to pay for QoL improvements as QoL falls.

2. ICER's proposed Clinical Trial Diversity rating system

It is critical to advance clinical trial diversity and incorporate health equity into value assessment. ICER has proposed a novel rating system to assess clinical trial diversity. However, this new measure has not been developed in a transparent way with broad stakeholder input. Given the barriers and complexity of enhancing clinical trial diversity, we advise ICER take additional time and follow a more well-established and rigorous approach to measure development before incorporating a novel rating system. The development of such a measure should also include evidence establishing the reliability and validity of the rating system, describe its limitations and determine criteria to define circumstances in which the absence of epidemiologic data, or limited US sample size, may prohibit its application. ICER should also recognize its system is unlikely to capture the full complexity of health disparities and underlying social determinants of health. The limited nature of proposed variables may result in the underrepresentation or neglect of certain racial/ethnic and socioeconomic groups, limiting the generalizability and applicability of the rating to more diverse populations. ICER should better describe the ways in which it envisions the rating stands to inform and advance health equity. In practice, ICER should commit to including the rating in its Draft Evidence Report to allow public comment. Evidence Reports should include a thorough discussion of trial diversity ratings so that stakeholders are clear on the assumptions, caveats and limitations of the data from which ratings are derived.

3. Subpopulation analyses

We appreciate ICER attempting to be more transparent about their selection of subpopulations to be evaluated by providing the rationale for including each subgroup. However, the appropriate subgroups can vary greatly by each trial, disease conditions and indication. In addition, for any analysis of subgroups that are not prespecified during trial design, results should be interpreted with extreme caution. Sample size often influences the effect modification of subgroups and therefore it can be challenging to detect effects reliably and replicate findings. Thus, we encourage ICER to include and engage in discussions with manufactures, clinicians and patients involved in reviewed trials that lead to sub-group definitions that are incorporated into ICER's assessments.

4. New methods for "non-zero" inputs

ICER recognizes the significance of incorporating the modified societal perspective in its assessments. ICER is moving towards modified societal analysis even if no data is currently available by using non-zero approach with data from the UK. However, labor markets in the US and UK may differ substantially. Thus, ICER needs to provide a clear

justification regarding the appropriateness and comparability of using UK settings for estimating lost patient and career time. In addition, ICER needs to incorporate the full range of benefits and impacts of a treatment, including non-traditional elements of value that are beyond the potential impact of productivity. This will avoid underestimation of the value of many innovative treatments. Thus, we encourage ICER to broaden its engagement process to include dedicated discussions with patients, clinicians, researchers and manufacturers to improve the rigor of estimating its modified societal prospective.

Comments on the value framework beyond proposed changes:

5. ICER’s Evidence Rating Matrix

The magnitude and certainty of health benefits are two different concepts that stakeholders (payers, clinicians, patients, etc.) may need to consider separately when making decisions regarding innovative technologies. Currently, ICER attempts to use a single rating scheme that combines the two concepts. The scheme includes 9 grades (A, B+, B, C+, C, C-, D, P/I, and I) and is operationally cumbersome. Conceptually, these grades are not straightforward to interpret, which is evident by questions asked by voters during ICER’s public deliberation meetings. To interpret each grade’s meaning, one has to refer back to the ICER rating matrix to figure out where the grade stands on the two domains (i.e., magnitude and certainty of health benefits). More importantly, from a decision maker’s perspective, a B+ rating may not necessarily mean “better” than a B rating and similarly, a C+ rating may not mean better than a C or C- rating. Which grade is “better” may depend on how the decision maker trade the magnitude for the certainty of health benefit. Therefore, we suggest ICER assess and report the magnitude and certainty of health benefits separately in its reviews. This is the approach taken by most of the major evidence assessment groups such as GRADE, AHRQ, Cochrane, and USPSTF.

6. Reporting and communicating data gaps and uncertainties

ICER acknowledges in its current Value Assessment Framework that it may use de novo evidence generation under certain circumstances where critical data elements are lacking; and that such analyses would be transparent to all stakeholders so that all participants can engage in deliberation on their validity and relevance. We applaud ICER’s effort to recognize circumstances in which data elements are lacking, necessitating the application of data that may lack desired rigor. However, we feel ICER can more explicitly and comprehensively describe potential implications of using such data, including uncertainties, potential biases and limitations of de novo analysis.

7. Societal perspective

ICER acknowledges that it is not reasonable to capture and estimate all benefits conferred to patients, their families, the health care system, public health or society from a clinical trial-based cost-effectiveness analysis (CEA) from a health care system perspective. ICER currently conducts CEA from both health systems and societal perspectives. However, the base case CEA, from which the health-benefit price benchmark (HBPB) is developed, is from the health system perspective. Given the diversity of intended stakeholders (patients, payers, caregivers, policy makers, academic researchers, etc.) it would be more appropriate to use a societal perspective as the base case of CEA.

Elevating the societal perspective to co-base aligns with recommendations 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 better incorporate into its reviews benefits that matter 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 ICER's press release should all be based on, or at a minimum include the societal-perspective CEA and HBPB. This will help further contextualize the assessment and ensure the relevance of the societal perspective is communicated to all consumers of ICER assessments.

8. Process for stakeholder input

We suggest ICER consider modifying the process to be more similar to the one used by CDC's Advisory Committee on Immunization Practices (ACIP). The ACIP has been established for 30+ years and has a transparent and well-accepted process for evaluation, recommendation and funding of new vaccines (<https://www.cdc.gov/mmwr/volumes/67/wr/mm6745a4.htm>). Manufacturers and academics are invited to present cost-effectiveness models which results in a robust and transparent discussion regarding differences in model structures and assumptions and the impact on model results and interpretation of results. We suggest that ICER include a member of ACIP on its steering committee and establish a process for inclusion of alternative approaches for economic modeling and allow presentation of manufacturer models. In addition, ICER should consider creating more opportunities for patient input throughout the entire review process. Patient groups should be consulted early in the process of model development to ensure their perspectives are incorporated into model assumptions and inputs.

9. Stakeholder engagement

ICER currently allows for stakeholder and manufacturer engagement at various timepoints throughout its value assessment process but does not afford those same stakeholders the opportunity to provide input on ICER's policy recommendations which are purportedly derived directly from the Policy Roundtable discussion. Given the complexity and range of topics typically discussed during the Policy Roundtable and their potential impact on patient access, its recommended ICER allow a stakeholder review and comment period prior to finalizing its policy recommendations. Such an approach would promote transparency and help ensure the final policy recommendations issued are an accurate reflection of the feedback and direction provided by the discussants. Engaging experts across the range of relevant disciplines will ensure ICER makes the most informed, balanced and appropriate recommendations and that the recommendations are contextualized as necessary. For example, when ICER proposes a step therapy approach with treatments that are not approved for the indicated population, considerations and implications should be clearly stated as there are several policy and patient implications. In addition, implications of delaying treatment should be carefully assessed and potential consequences described when recommending a step therapy approach.

10. Improve approach to eliminate bias and maintain balance during public meetings

To preserve the integrity of ICER's value assessment process, every effort should be made to remain unbiased in its approach, from the selection of comparators and relevant outcomes to the identification of the most relevant policy questions during its Policy Roundtable discussions. ICER should refrain from excessive editorializing during its public meetings, particularly leading up to and during appraisal committee voting. Voters should be encouraged to ask clarifying questions leading up to voting but ICER should avoid providing its subjective characterization of value or revisit its rationale for Net Health Benefit rating until after all votes have been cast for all questions. Lastly, ICER should make an effort to ensure deliberative time is not disproportionately dedicated to presenting the perspectives and interests of certain stakeholders at the detriment of others. We encourage ICER to strive for an equitable process, inclusive of stakeholder perspectives and one that prioritizes the lived experiences of patients and their families.

Sincerely,

Mark Marsico, PhD, MPH
Director
Center for Observational and Real World Evidence

Institute for Clinical and Economic Review (ICER)

Submitted: publiccomments@icer.org

Re: 2023 Value Assessment Framework- Proposed Changes

June 30, 2023

To whom it may concern:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER)'s request for input and comments on the proposed changes regarding the 2023 Value Assessment Framework. It is timely and we appreciate the recognition of the importance of considering diversity in the assessments of any healthcare product. We also appreciate the openness of the organization to public comment.

The MRCT Center is a research and policy center that addresses the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. While the MRCT Center often collaborates and interacts with FDA, we have not discussed the comments provided herein with anyone at FDA. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.*

The proposed modifications to the Value Assessment Framework ("the Framework") does not replace but updates the Framework to ensure currency. The MRCT Center particularly appreciates the detail and instruction of the proposed changes; we commend ICER and endorse many of recommendations and proposals. Specifically, we value the attention paid to:

- Transparency not only of the changes proposed but also to the logic and reasoning behind those changes
- The importance and criticality of clinical trial diversity, representativeness, and other dimensions of health equity
- The challenge of developing value assessments when data on disease-specific prevalence estimates by demographic are not available
- The challenge of value assessments for the US population that are based on data derived from global clinical trials

* Brigham and Women's Hospital, Ropes and Gray LLP, Harvard Medical School, and Harvard University.

- The tension between ICER's Framework that analyzes evidence relevant to the population versus decision-making for individual patients
- The appreciation that ICER's focus on and attention to clinical trial diversity will animate further progress toward representation.
- The creation of an ICER Patient Council
- The inclusion of caregiver time, burden, and quality of life in value calculation.

In the context of enthusiastic support for the proposed changes, the MRCT Center has a number of considerations and further thoughts for ICER to consider:

- It would be helpful to understand which non-health impacts are being considered, and how those non-health impacts affect different populations. Are the non-health impacts free from bias? What are the measures being used? Are the measures themselves free from bias?
- In the utilization of a "human capital approach," is value assessed or attributed if a person is not in the "formal" or "informal" labor force? How is productivity measured and valued for those not in the labor force?
- We remain critical of the use of QALYs as they devalue the lives of people with disabilities. Should QALYs themselves be replaced? Are there more appropriate alternatives that value lives equivalently? QALYs are also inadequate for pediatric assessments.
- The focus appears principally to be race and ethnicity, but only 4 categories are rated (Table 2.2). The limited categories of race and ethnicity currently endorsed by OMB are problematic; we trust that if OMB restates the categories, ICER will reassess. But we also believe that ICER could bring an independent lens to these problematic groupings rather than concretize categories that we know are inaccurate and insufficient, expand the rating categories, and broaden the representation score. Specifically:
 - Awarding additional value if sponsors focus on and achieve representative participation of relevant subpopulations for the condition (e.g., pediatric populations, LGBTQI+ populations, etc.)
 - Attention to social determinants of health (SDoH) and the value of inclusive populations that represent different SDoH populations
 - Inclusion of pediatric populations
 - Inclusion of people with disabilities
- Are race/ethnicity valued equivalently to sex (and age)? Table 2.2 appears to value race/ethnicity as having greater significance and weight than other parameters.
- We encourage ICER—and pharmaceutical companies—not only to justify (and value) inclusion of some subgroups but also justify exclusion of others.

Three overarching considerations that we wish ICER to consider:

- It is well known that **pediatric populations** are understudied and underserved. People under that age of 18 are often not included in clinical trials even when the potential treatment is directly relevant to them. Evidence of safety and efficacy—no less of value—of therapeutic interventions for pediatric indications is lacking. We strongly

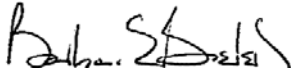
advocate that ICER include pediatric representation in their revision and in their value assessment. In addition, please consider:

- Mention pediatric populations in the definition of clinical trial diversity: “*ICER will provide an overall diversity rating for the following demographic characteristics: race/ethnicity, sex, and age, specifically, adults aged 65 and older...*” Here and throughout the document, there is an opportunity to strengthen the inclusion of pediatrics
- Call out pediatric subpopulations as an underserved population of interest
- The Medicare-eligible population is specifically identified for dynamic pricing for small molecule and biological products. Mention of and applicability to pediatric populations would be beneficial.
- The patient engagement program presents multiple opportunities for the inclusion of adolescents and young adults and for parents/guardians of children too young or otherwise able to represent themselves.
- The rating categories in Table 2.2 specify and value age specified when age includes “Older Adults (≥ 65). Here there is an opportunity to include categories for pediatric populations.
- It would be helpful to include special pediatric considerations, including the valuation of productivity for both patient and carer in Table 3.1.
- Will ICER conduct a dynamic pricing scenario for small molecule and biological products that are predominantly targeted to pediatric populations as well?
- Similar to pediatric populations, **people with disabilities** are the most prevalent underserved population and, frankly, data on disabilities is rarely collected in clinical trial demographic information. It would be helpful for ICER to call out this population, to ensure that all materials and communications are accessible and that all meetings accommodate people with disabilities.
- The term shared **decision-making** recurs in the document. We feel that it is important to emphasize that the decision to participate in a trial, or to avail oneself later of an approved intervention is indeed the participant’s or patient’s decision. It would be helpful to reframe the concept of decision-making as one that belongs to the participant or patient, after discussion with the provider, and with the assistance of a supporter for supported decision-making when requested.

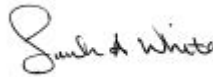
Thank you again for the opportunity to comment on the proposed changes to the ICER Framework. We believe that the ICER has taken an important step in calling further attention to the importance of clinical trial diversity. That participant demographic representativeness should align with disease-specific prevalence estimates is foundational to understanding the heterogeneity of treatment effect and thus of the value assessment. The proposed changes will bring attention to these important topics. The questions and considerations we mention are intended to enhance the process and bring attention to other underserved populations, including children, adolescents, young adults, people with disabilities, and others.

Please feel free to contact the MRCT Center (bbierer@bwh.harvard.edu,
sawhite@bwh.harvard.edu, or mark.barnes@ropesgray.com) if we can be helpful or if you wish
to discuss.

Respectfully submitted,



Barbara E Bierer, MD
Faculty Director, MRCT Center



Sarah A White, MPH
Executive Director



Mark Barnes, JD, LLM
Faculty Co-Director



Our Mission: To drive efforts to cure psoriatic disease and improve the lives of those affected.

June 30, 2023

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800,
Boston, MA 02108

Dear Dr. Pearson,

Thank you for the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) proposed changes to the 2023 Value Assessment Framework. The National Psoriasis Foundation (NPF) has been a leader in supporting patient engagement in the ICER process, and we recognize the importance of developing evidence-based approaches to inform value. The NPF has had the unique experience of participating in both a value assessment on systemic psoriasis therapies in 2016, and a condition update in 2018.

Psoriatic disease is a heterogenous, immune-mediated condition that affects over eight million Americans. While psoriatic disease primarily affects the skin, most patients have evidence of systemic inflammation which increases their risk for the development of many comorbidities. For example, approximately one-third of psoriasis patients have or will go on to develop psoriatic arthritis with severe pain and/or irreversible bone loss. Psoriatic disease is also associated with several co-occurring conditions such as cardiovascular disease including stroke and hypertension, diabetes, metabolic syndrome, depression/anxiety, and cancer.

We offer the following comments now as part of our continued commitment to elevating the experience of individuals living with chronic diseases in value assessment:

- **The Use of Multiple Cost-effectiveness Outcome Measures:** As NPF has urged in the past, we challenge ICER to further evolve the framework to incorporate multiple cost-effectiveness outcomes measures. We continue to stress the challenge of measuring a chronic disease such as psoriatic disease with the measures and tools available today.
- **An increased focus on clinical trial diversity:** This will encourage developers to assess their health technology across the full breadth of the American population including underserved and underrepresented populations.
- **Assessing non-zero impacts on patient and carer productivity:** Too often, treatment efficacy focuses on biomarkers but not the patient and their family's overall wellbeing.

Applying a non-zero impact on patient and carer productivity is a step towards better reflecting the realities of the American population.

- Improved patient engagement: NPF appreciates ICER's recognition of the time demands placed on community leaders that engage in the ICER process. We support the proposed solutions including:
 - Compensating patients for engaging in small group discussions and public meetings as other "experts" have been compensated.
 - Continuing the use of small group discussions to solicit input.
 - Creating a Patient Council to provide input on ICER's patient engagement strategy. We suggest the Council's authority and oversight be transparently shared with the patient community.
- Real World Evidence: We appreciate ICER's openness to seek opportunities to use real-world evidence within assessments, including comparative clinical effectiveness and in the design of economic models.

Thank you for your consideration of our views. We remain committed to ensuring that the perspectives of all individuals living with psoriatic disease (and the chronic disease community) are properly considered and reflected in the value of therapies. For additional information, or if we can be of further service, please contact Sarah Buchanan, Director of Federal Government Relations and Health Policy, at sbuchanan@psoriasis.org.

Sincerely,

A handwritten signature in black ink, appearing to read "Jason Harris". The signature is fluid and cursive, with a large initial "J" and "H".

Jason Harris
Vice President, Advocacy and Government Relations
National Psoriasis Foundation



NATIONAL HEALTH COUNCIL

June 30, 2023

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review (ICER)
14 Beacon Street, Suite 800
Boston, MA 02108

Re: 2023 Value Assessment Framework: Proposed Changes

Dear Dr. Pearson,

The National Health Council (NHC) is pleased to provide the following comments in response to the 2023 Value Assessment Framework Proposed Changes. The ICER's Value Assessment Framework can have significant effects on NHC-member patient advocacy groups and their constituent populations, many of whom have been through past ICER reviews. The NHC is appreciative that ICER has updated its framework and released the changes for public comment.

Created by and for patient organizations more than 100 years ago, the NHC brings diverse organizations together to forge consensus and drive patient-centered health policy. We promote increased access to affordable, high-value, sustainable health care. Made up of more than 150 national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient organizations. Other members include health-related associations and nonprofit organizations including the provider, research, and family caregiver communities; and businesses representing biopharmaceutical, device, diagnostic, generic drug, and payer organizations.

Clinical Trial Diversity

Under proposed changes in Sub-Section 2.1, Clinical Trial Diversity, the NHC suggests expanding the criteria described in Table 2.2. Under race and ethnicity, we suggest including American Indian/Alaskan Native (AI/AN) Indigenous representative groups. Under the sex category, we suggest including non-binary classification, and in relation to the age category, we recommend stratifying across age groups rather than exclusively aggregate data in clinical trial participants over the age of 65. Particularly, the age category would amplify the intent of ICER to focus on diversity as varied age group participation may yield differential outcomes measures. AI/AN representative groups classification is imperative particularly due to reduced sample size reporting and future investment for targeted clinical trial recruitment.

Expanded sex classification is congruent to the broader understanding of LGBTQ+ clinical trial representative participants. No mention was provided in the proposed changes nor the white paper on *Advancing Health Technology Assessment Methods that Support Health Equity* of clinical trial participants with differential abilities. ICER should consider adding this category for classification purposes and expansion of diversity metrics.

Lastly, we suggest outlining how the proposed changes to this framework on clinical trial diversity complements the US Food and Drug Administration's (FDA's) ongoing work on creating advisory councils and other initiatives that account for patient centricity and transparency. Also, the FDA guidance "Collection of Race and Ethnicity Data in Clinical Trials (October 2016)" and, "[*Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials*](#)." have robust suggestions on increasing diversity in clinical trials for sponsors and drug developers. It is unclear how ICER's Clinical Trial Sample Diversity Ratings would build upon these guidances. As an organization with a diverse membership of multiple patient advocacy organizations and biotech and pharmaceutical companies, we believe these new changes could lead to confusion and duplicative efforts.

Subpopulation Analyses

Under the proposed changes 2.2.1, subpopulation analyses, the NHC suggests that ICER rely primarily on interviews with patients, caregivers, and recommendations from patient advocacy groups. Targeted literature reviews and advice from clinical experts are helpful but may impose preconceived interpretations that are not in line with current patient experiences. Non-patient provided information should be considered secondary, after first-hand patient input is given.

Patient Engagement Program

The NHC applauds ICER's efforts to update its patient engagement program. Patient engagement is not only important to capturing the true value of treatments, but it is also essential to fully understanding the impacts, costs and benefits, and outcomes that are important to patients and family caregivers. The suggested accessibility and inclusive design of public meetings is an impactful step that ICER can take to increase participation of those with chronic diseases and disabilities in ICER meetings.

The NHC is appreciative of the addition of honoraria for patient and caregiver participants in ICER's patient engagement work. Compensation is an important driver of diverse patient participation, especially as many patients who are hourly wage earners, do not have paid leave, or have elder or childcare-giving responsibilities. In 2020, the NHC published its [*Fair-Market Value Calculator and Compensation Toolkit*](#) on compensation for patient, caregiver, and patient advocacy group engagement that includes a calculator for "an estimated, reasonable, and fair hourly compensation range."¹ The NHC encourages ICER to use this toolkit, including the calculator, as a reference when determining a fair-market value compensation range for patient engagement activities.

The NHC is excited about the creation of a new Patient Council to reflect ICER's commitment to diverse and inclusive patient participation in the value assessment space. The NHC suggests that ICER publishes how it recruited and chose the patient advisors, as well as list any relevant affiliations the patients have. The NHC further suggests that the Council's authority and

¹ National Health Council, "Patient Compensation Tools," National Health Council, June 25, 2020, <https://nationalhealthcouncil.org/additional-resources/patient-compensation-tools/>.

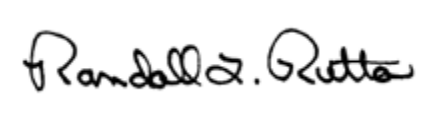
oversight be transparently shared with the patient community – including how suggestions by the Council have been incorporated into practice. Good practice guidelines for patient engagement (including engagement with a Patient Council) can be found in the [NHC’s Rubric to Capture the Patient Voice](#).²

Conclusion

We deeply appreciate ICER’s commitment to value assessment. We hope that our suggestions are taken into consideration as you continue enhancing a framework that reflects patient engagement and centrality.

Please do not hesitate to contact Omar A. Escontrías, DrPH, MPH, Senior Vice President, Equity, Research & Programs, if you or your staff would like to discuss these issues in greater detail. He is reachable via e-mail at oescontrias@nhcouncil.org.

Sincerely,



Randall L. Rutta, MA
Chief Executive Officer

² National Health Council, “The National Health Council Rubric to Capture the Patient Voice: A Guide to Incorporating the Patient Voice into the Health Ecosystem.” (Washington, DC, June 2019), https://www.nationalhealthcouncil.org/wp-content/uploads/2019/12/NHC_Patient_Engagement_Rubric.pdf.



Institute for Clinical and Economic Review (ICER)
14 Beacon St., Suite 800
Boston, MA 02108

RE: 2023 Proposed Revisions to Value Assessment Framework

On behalf of the more than 25 million Americans living 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 ICER's 2024 Value Assessment Framework (VAF).

NORD is a unique federation of non-profits and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD was founded 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing that landmark law. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of and access to comprehensive, affordable health care services.

ICER's long history and experience with health technology assessment (HTA) gives it a considerable voice in the discussion of cost-effectiveness of treatments and NORD is grateful for ICER's ongoing efforts to incorporate stakeholder feedback and consistently revise and refine its framework. Cost-effectiveness assessments are of particular interest and importance to the rare disease community, given the high level of unmet need and high cost of treatments.¹ Given the ever-changing landscape of health care, it is important to continue sourcing feedback from all stakeholders on the most effective inputs for refining value assessments.

NORD thanks ICER for the opportunity to comment on the proposed revisions to the Value Assessment Framework and would like to provide the following specific recommendations:

Recommendation 1: NORD supports efforts to strengthen trial diversity and subgroup analysis; given the newness of the metrics and approaches, we recommend ICER carefully assess the differences in the applicability of this VAF for rare vs. more common diseases and continue to refine the framework in future revisions as needed based on incremental learnings.

Diversity in clinical trials

NORD commends the increased focus on diversity for clinical trials. Evidence demonstrates that the inclusion of diverse participants in clinical trials has a positive impact on patient outcomes, particularly for rare diseases. However, for many rare diseases, overall and sub-group specific disease prevalence is not well understood. Of particular challenge to the rare disease community is the time from the onset of

¹ Althobaiti, H., Seoane-Vazquez, E., Brown, L. M., Fleming, M. L., & Rodriguez-Monguio, R. (2023). Disentangling the Cost of Orphan Drugs Marketed in the United States. *Healthcare (Basel, Switzerland)*, 11(4), 558. <https://doi.org/10.3390/healthcare11040558>

symptoms to initial diagnosis, known as the diagnostic odyssey.² A NORD survey conducted in 2019 found that it takes rare disease patients on average 5 or more years to be correctly diagnosed, while taking up to 10 years in some cases.³ Barriers to diagnosis are even greater amongst nonwhite communities and communities with limited English proficiency. Issues of economic inequality abound in the diagnosis and treatment space as well. The average rare disease patient will see around 7 different physicians prior to receiving a correct diagnosis, which in itself can result in significant financial hardship for some families.⁴

Finally, the inclusion of an age-based diversity metric is often more complicated and may not be appropriate for some rare diseases patients, as between 50-75% rare diseases manifest beginning in childhood.⁵ As rare disease can result in life-encumbering symptoms, for too many rare diseases the relative fraction of patients that live long enough to be captured in the 65+ category is much lower than for the general population.

In order ensure rare disease products are not unjustly devalued by being held to an impossible-to-meet clinical trial standard, NORD has the following recommendations:

1. **Carefully assess potential limitations in applying diversity evaluations for clinical trials for orphan drugs.** While NORD is supportive of efforts to enhance trial diversity the data scarcity and unique challenges of rare disease drug development need to be considered to ensure orphan drugs are not unintentionally and unjustly penalized.
2. **Reconsider the proposal to use the US census population distribution in lieu of prevalence estimates when prevalence data is lacking.** Many rare diseases are unlikely to be distributed exactly proportionally to the U.S. census population. For instance, around 80% of rare disease have some genetic component, increasing their likelihood of occurrence in certain groups of individuals based on their genetic descent.⁶ Similarly, many rare disease patients must travel long distances to see specialists familiar with their disease, and many, in particular in rural areas, ultimately relocate to be closer to appropriate medical care. 17% of survey respondents indicated they had considered moving or had move to be closer to medical care.⁷ Moreover, the scarcity of robust prevalence and natural history data and the small sample sizes make overall extrapolations based on census data highly error-prone for rare diseases.
3. **Align with and incorporate learnings from FDA and NIH on how to capture, assess and report clinical trial diversity – in particular for rare diseases.** Multi-year efforts have been underway at both FDA and NIH to increase clinical trial diversity. More recently, as part of the last Prescription Drug User Fee Act (PDUFA), FDA now has to increase the transparency and reporting of clinical trial diversity metrics for trials that support product reviews, and sponsors have to proactively assess and increase the diversity in their trials. Similarly, pending regulation would require NIH to do the

² Marwaha, S., Knowles, J.W. & Ashley, E.A. A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. *Genome Med* **14**, 23 (2022). <https://doi.org/10.1186/s13073-022-01026-w>

³ *What You Should Know About Undiagnosed Rare Diseases | NORD*. (2022, July 27). National Organization for Rare Disorders. <https://rarediseases.org/understanding-rare-disease/undiagnosed-diseases/>

⁴ Ronicke, S., Hirsch, M. C., Türk, E., Larionov, K., Tientcheu, D., & Wagner, A. D. (2019). Can a decision support system accelerate rare disease diagnosis? Evaluating the potential impact of Ada DX in a retrospective study. *Orphanet journal of rare diseases*, *14*(1), 69. <https://doi.org/10.1186/s13023-019-1040-6>

⁵ Bavisetty, S., Grody, W. W., & Yazdani, S. (2013). Emergence of pediatric rare diseases: Review of present policies and opportunities for improvement. *Rare diseases (Austin, Tex.)*, *1*, e23579. <https://doi.org/10.4161/rdis.2357>

⁶ National Human Genome Research Institute. Rare Genetic Diseases. *National Human Genome Research Institute*. (2018.) <https://www.genome.gov/dna-day/15-ways/rare-genetic-diseases>

⁷ NORD (2020). Barriers to Rare Disease Diagnosis, Care and Treatment in the US; National Organization for Rare Disorders. https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf

same for NIH-funded research.⁸ ICER should align the diversity framework and metrics with the metrics used by FDA and NIH to the extent possible to increase overall transparency. Moreover, as FDA and NIH increase their understanding of the strength and limitations of these metrics, and how they shape the make-up of clinical trials, ICER should work closely with these agencies to benefit from these learnings and refine the framework.

Subgroup analysis

NORD supports ICER's efforts to increase subgroup analysis. However, given the unique challenges and limitations of rare disease drug development outlined above, subgroup analysis may be more difficult – and in some cases impossible – for rare diseases. NORD urges ICER to continue to evaluate to what extent the subgroup analysis approaches must be revised for rare diseases. For instance, subgroup analyses based on disease stage or disease subgroup (e.g., specific underlying genetic mutation) may be more meaningful for many rare diseases than subgroup analyses based on age, and to the extent that the ICEMAN tool has not been fully validated for rare disease trials, we urge ICER to do so to ensure consistency.

Recommendation 2: ICER should partner with patient groups and leverage best practices for effective patient engagement that captures the diversity of patient voices.

NORD supports the proposal to increase patient accessibility measures by creating an online portal for submission of patient comments, formalization of small-group patient and caregiver discussions and creation of a patient council. Researchers suggest that involving patients with rare disease may increase the quality and relevance of these studies.⁹ However, the revised VAF lacks clarity on how these proposed increased patient accessibility measures would be implemented. NORD has concerns that an ineffective implementation of the proposed increase in accessibility measures would not allow for meaningful patient contribution.

To maximize the impact of patient data submissions, ICER should include learnings from other organizations who collect patient survey data, such as FDA's reports on using patient experience data in regulatory decision making, on collecting quality, actionable and heterogenous patient data.¹⁰ Specifically, NORD has identified these main areas of concern regarding the collection of patient data:

- a. **Standardization of questions across stakeholders to elicit a diversity of robust and reproducible responses from different patient communities.** While the existing online patient experience submission form is a step in the right direction, the proposed questions are overly broad and will likely be difficult to render into an actionable form.
- b. **Demonstration of meaningful contribution.** Given the guidance in the proposed VAF and former assessments published by ICER, there is limited insight into how patient experience submission will be used to influence cost-effectiveness decision making.

⁸ NIH Clinical Trial Diversity Act of 2023, H.R. 3503, 118th Congress (2023) <https://www.congress.gov/bill/118th-congress/house-bill/3503?s=1&r=1>

⁹ Velvin S., Hartman T., Trine Bathen., Patient involvement in rare diseases research: a scoping review of the literature and mixed method evaluation of Norwegian researchers' experiences and perceptions, *Orphanet journal of rare diseases*. 17 (212), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9158134/#:~:text=Involving%20patients%20with%20rare%20diseases,the%20rarity%20of%20their%20diseases.>

¹⁰ Center for Drug Evaluation and Research. *Assessment of the use of patient experience data*. U.S. Food and Drug Administration. <https://www.fda.gov/drugs/development-approval-process-drugs/assessment-use-patient-experience-data-regulatory-decision-making>

- c. **Transparency of evaluation.** Similar to the above comment, there has been historically limited insight into how patient experience data is being combined with other measures of value. We strongly encourage a greater promotion of transparency in how much of an impact patient participation in the valuation process will have.

In order ensure a smooth implementation of the proposed new accessibility measures, NORD has the following recommendations:

1. **Partner with the relevant patient communities who would benefit most from the proposed accessibility measures to pilot test the options to see what works and what does not.** This could include partnering with patient groups to identify interested prospective candidates with a diversity of backgrounds.
2. **Explicitly and transparently publish the rationale for which communities are selected to participate on the patient council.** NORD strongly recommends inclusion of a patient with a rare disease on the council, due to the unique perspective the rare community brings on value assessment.
3. **Apply increased scientific rigor to the patient data collected to ensure it may be used quantitatively or qualitatively in analysis.**

Recommendation 3: ICER should develop further guidance and best practices on the appropriate use of RWE, in particular for rare diseases.

As referenced above, the paucity of available data for patients with rare diseases makes research and evaluations particularly difficult. Real-world evidence (RWE) can help to supplement existing randomized controlled trials (RCTs) and other existing medical literature in a way that provides robust and reliable evidence and helps capture patient experiences with a therapy. NORD is supportive of continued efforts to use RWE in the value-assessment framework, though believes there is an opportunity for further refinement in the use of RWE specifically in the evaluation of rare diseases.

RWE can come from many sources outside of the traditional RCT structure, including electronic health records (EHRs) and claims, patient-generated data, product and disease registries, and more. RWE may be incorporated throughout the clinical trial process, as well as generated post approval. As noted in the existing VAF, RWE can have limitations, though in the rare disease space the benefit of use often greatly outweighs the cost.

Although there have been a number of recent, high-profile natural history studies done on some rare diseases, including Duchenne muscular dystrophy, spinal muscular atrophy and Huntington's disease, to name just a few, the vast majority of rare diseases lack any benchmark for disease progression. RWE can help to bridge the gap in knowledge between current and projected disease state for a patient. While RCTs remain a crucial tool in the study of pharmaceutical products, they may not be representative of real-world clinical practice, particularly for a population as heterogenous as the rare disease community.¹¹

In order ensure appropriate use of RWE in assessments for rare disease therapies, NORD has the following recommendations:

¹¹ Liu, J., Barrett, J. S., Leonardi, E. T., Lee, L., Roychoudhury, S., Chen, Y., & Trifillis, P. (2022). Natural History and Real-World Data in Rare Diseases: Applications, Limitations, and Future Perspectives. *Journal of clinical pharmacology*, 62 Suppl 2(Suppl 2), S38–S55. <https://doi.org/10.1002/jcph.2134>

1. **NORD encourages the finalized versions of the VAF to include increased granularity on how RWE will be evaluated relative to other methods of collecting clinical data.** ICER's current value-assessment framework contains little guidance into how RWE will be incorporated into its analysis of products. Though the publishing of its learnings from the 24 month RWE pilot were a step in the right direction, there remains little public information into how the VAF uses RWE in the analysis – and the challenges of rare disease drug development create unique challenges for RWE in this space.
2. **Due to the lack of available data for rare diseases, we encourage future revisions to the VAF to specify that products with fewer available trial participants will not be de-valued due to lack of historical data.**

Recommendation 4: ICER should continue to revise and refine the VAF as the science evolves and the healthcare landscape changes.

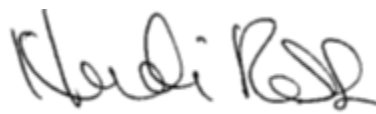
As outlined above, the science and health care landscape continues to evolve and NORD is encouraged by ICER's efforts to update and refine the VAF to ensure it continues to be relevant and effective. In order ensure the VAF remains scientifically accurate and feasible in the future, NORD has the following recommendations:

1. **Continue to assess the best and most practical approach and metrics to capture economics and value.** We recognize that QALYs and evLYGs hold a significant place in the existing health technology assessment (HTA) infrastructure, but we encourage ICER to continue evaluating their use as we are not convinced that continuing to use the QALY or the evLYG is scientifically appropriate or in the best interest of rare disease patients. NORD strongly encourages the development of value assessments based on fair, equitable and transparent metrics.
2. **Continue to assess how the Inflation Reduction Act impacts the drug development and reimbursement landscape and refine the VAF accordingly.** The Inflation Reduction Act (IRA) will impact the drug development and reimbursement landscape in complex and hard-to-predict ways. While we agree that incorporating the impact of the IRA in the VAF will be important, CMS has not to date finalized the details of the negotiation program implementation and the ultimate impacts on the ecosystem remain hard to predict.

We again thank ICER for the opportunity to comment and look forward to working with ICER to ensure rare disease patients can fully participate in and benefit from the Value-Assessment Framework. For questions related to this letter, please contact Karin Hoelzer, Director of Policy and Regulatory Affairs at KHoelzer@rarediseases.org or Heidi Ross, Vice President of Policy and Regulatory Affairs at HRoss@rarediseases.org.



Karin Hoelzer, DVM, PhD
Director, Policy and Regulatory Affairs
National Organization for Rare Disorders



Heidi Ross, MPH
Vice President, Policy and Regulatory Affairs,
National Organization for Rare Disorders

30 June 2023

VIA ELECTRONIC DELIVERY

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, Massachusetts 02108

Re: 2023 Value Assessment Framework Proposed Changes

Dear Dr. Pearson,

Novartis Services, Inc. submits this letter on behalf of Novartis Pharmaceuticals Corporation and its affiliates referred to collectively herein as “Novartis” and appreciates the opportunity to comment on the proposed changes to the Institute for Clinical and Economic Review’s (ICER) Value Assessment Framework (VAF).

Novartis provides health care solutions that address the evolving needs of patients and societies worldwide. Our broad portfolio of medicines includes treatments in the areas of neuroscience, immunology, hepatology, dermatology, respiratory, cardiovascular, renal, metabolism, oncology, immuno-oncology, chimeric antigen receptor (“CAR”) T-cell therapies, radioligand therapy, and gene therapies. At Novartis, we are united by a single purpose to reimagine medicine to improve and extend lives. Through innovative science and technology, we address some of society’s most challenging health care issues. We work to discover and develop breakthrough treatments and find new ways to deliver them to as many people as possible. Our vision is to be the most valued and trusted medicines company in the world.

Novartis supports the value of its products through rigorous science-based evidence generation. It is important that ICER’s attempts at value assessment, as reflected in the VAF, be based on sound methods, reflect the high degree of uncertainty underlying its evaluations to provide context to the diverse set of health-care decision makers, and be firmly rooted in a patient-centric approach. Novartis is concerned that ICER’s latest proposed VAF deviates from these principles in several ways. Our comments reflect an effort to help ICER improve its VAF to better reflect those principles. Below is a summary of the key points:

- I. ICER’s proposed methods for value assessment, including the use of cost-effectiveness, its budget impact assessment, and “shared-savings” model, obscures the full value of the products reviewed by ICER and increases decision-making uncertainty.
 - a. Perspective: ICER continues to rely on a payer perspective for its base-case, and use of a “modified” social perspective. ICER should use the recommended societal perspective as its base-case, per established health economic guidelines.¹

- b. Other elements of value: ICER is selectively choosing some elements of value (productivity) while ignoring other well-established elements of value with limited scientific basis for its selections.²⁻¹³
 - c. Denominators: Use of the (QALY) and the (evLYG) are fraught with well documented limitations. If ICER chooses to continue to use these measures, they should be much more circumspect in their conclusions and be more transparent with the limitations and uncertainties. ICER should also continue to explore alternative methods that account for these limitations.¹⁴
 - d. Thresholds: ICER should avoid all use of arbitrarily low thresholds such as the proposed \$50,000 to \$100,000 per QALY or evLYG to make determinations of a product's value.
 - e. Shared savings model: Presumes to provide context for "shared-savings" but does not reflect the overall consumer surplus during an entire product's lifecycle.
 - f. Budget impact model: Arbitrary determination for "budget warnings".
- II. ICER should re-double its efforts around diversity and inclusion as well as sub-population analyses, but the current proposed manifestation is problematic.
- a. ICER should consult with patients, manufacturers, and other relevant groups to create evaluations that are more inclusive. ICER should hold off on inclusion of the proposed ratings until more appropriately informed and validated methods are established.
 - b. ICER should also account for additional evidence, including subsequent clinical trials and real-world evidence (RWE) that come later in a product's life cycle, to more fully reflect manufacturers' attempts to address these issues. This must include fit-for-purpose methods and processes.
 - c. Sub-population analyses should be based on the underlying disease epidemiology and relevant groups should be identified with consultation of patient-groups, manufacturers, and other important stakeholders.
- III. ICER's efforts to improve patient-voice in its value determination are a step in the right direction; however, they fall short of best-practices and ICER should make truly meaningful changes to include patient groups throughout the assessment process, including having relevant patients/advocacy group representatives as standing voting members of its assessment committees.¹⁵⁻¹⁷
- IV. Changes to the ICER framework reflect a trend towards less consultation rather than improved consultation. ICER should have a more robust input session around proposed changes to its value assessment framework that includes adequate time for feedback and engages relevant experts, health care decision makers, manufacturers, payers, and patients.

We appreciate ICER's consideration of our proposed changes and believe that better, comprehensive, and balanced understanding of the value of the innovations that manufacturers, like Novartis, introduce will ultimately result in a better health-care system and most importantly improved patients' lives. A more detailed set of recommendations are provided below.

- I. ICER's proposed methods for value assessment, including the use of cost-effectiveness and the "shared-savings" model, obscures the full value of the products reviewed by ICER and increases decision-making uncertainty.

- a. **Model Perspectives:** ICER’s base case models should be from the societal perspective according to current health economic guidelines. Reliance on models based on the payer perspective, as well as the “modified” societal perspective, by design, exclude considerations of other aspects of value. Every attempt should be made to generate baseline models that seek to capture all aspects of value, and discuss limitations around areas where assumptions are needed, rather than excluding them by design. Sensitivity analyses using other perspectives can then be easily achieved to help different decisions makers.
- b. **Elements of Value:** ICER’s attempt to include estimates of productivity losses is a step in the right direction, however the choice to not include other established elements of value is concerning. Assigning "non-zero" inputs for productivity impacts, even in the absence of direct data, introduces subjectivity and potential biases into the cost-effectiveness analyses. This could lead to uncertainties and disputes regarding the accuracy and reliability of the results.
- Additionally, there continues to be significant efforts to quantify other dimensions of value.²⁻¹³ For example, one of the key challenges for rare diseases is how to value incremental improvements in patients with advanced disease where small incremental improvements make a huge difference in their lives (e.g., ability of an ALS patient to use fingers to communicate on a device and/or move an electric scooter) but seems very small compared to overall disease continuum. This is especially true for rare diseases with significant disability and where therapies will not reverse disease course. The decision not to quantitatively weigh additional dimensions of value in the reference case incremental cost-effectiveness findings may limit the ability to fully capture and compare the value of different treatments. This could potentially lead to an incomplete assessment of the benefits and drawbacks of specific therapies, especially when there are trade-offs between different value elements. ICER’s latest proposals for modifications to the VAF do not reflect these concerns and the latest methodological advances in value determinations. ICER’s proposal to attempt to quantify productivity losses should also be extended to the other established aspects of value, but through a robust consultation with relevant experts, manufacturers, patients, and other key health care decision makers.
- c. **Summary Benefit Denominators:** ICER’s reliance on the use of summary benefits measures, such as the Quality-adjusted life years (QALYs) and the equal-value of Life Years Gained (evLYG) have well-documented limitations. If ICER chooses to continue to use these types of benefit summary measures, they should be much more circumspect in their conclusions and be more transparent with the related limitations and uncertainties. ICER should also continue to explore alternative methods that account for these limitations.¹⁴
- d. **Cost-effectiveness Thresholds:** ICER should avoid all use of arbitrarily low thresholds such as the proposed \$50,000 to \$100,000 per QALY or evLYG to make determinations of a product’s value. As noted by ICER there is a high degree of uncertainty as to whether these thresholds truly reflect patients’ and societies’ preferences. Additionally, these measures have been shown to have problems with bias against certain groups (elderly, disabled, etc.). This uncertainty warrants more flexibility, and the presence of arbitrarily low thresholds may do more harm by potentially undervaluing much needed therapies for patients. ICER acknowledges ongoing research on cost-effectiveness thresholds and the need for further discussion with academic experts and stakeholders. ICER should adopt more flexible and appropriate methods that directly address these known limitations.

- e. **Shared Savings Model:** ICER should discontinue its use of the “shared-savings” model. This model relies on untested assumptions, in particular, around so-called “fair” shared savings. Further investigation, in consultation with patients, payers, manufacturers and relevant experts is warranted.
- II. ICER should re-double its efforts around diversity and inclusion as well as sub-population analyses, but the current proposed changes have some clear limitations.
- a. **Diversity in Evidence:** ICER proposes to report a “Clinical Trial Diversity” measure by using a Participant to Disease Prevalent Ratio (PDRR) and generate ratings of “Good”, “Fair”, and “Poor” around demographic characteristics such as race/ethnicity, age and sex. All efforts should be made to improve the inclusivity of clinical trials to represent the underlying demographics of patients suffering with a disease. However, ICER’s choice of cut-offs and score weightings are completely arbitrary. The arbitrary nature of these categorizations set only by ICER are highly problematic. The scoring system based on estimated participation-to-prevalence ratios may oversimplify the complexity of achieving true diversity in clinical trials. It does not fully account for various factors that influence participation, such as socioeconomic factors, cultural considerations, and regional differences. ICER should consult with patients, manufacturers, and other relevant groups to create evaluations that are more inclusive and ICER should hold off on inclusion of these ratings until better methods are established and account for other activities manufacturers are undertaking around diversity in evidence, including RWE and follow-on clinical trials.
 - b. **Inclusion of RWE:** ICER should also account for additional evidence, including subsequent clinical trials and RWE that comes later in a product’s life cycle, to more fully reflect manufacturers attempts to address these issues. This must include fit-for-purpose methods and processes.
 - c. **Sub-populations:** Sub-population analyses should be based on the underlying disease epidemiology and relevant groups should be identified with consultation of patient-groups, manufacturers, and other important stakeholders. Additionally, for rare diseases and many other diseases, subpopulation poses a challenge in that trials are small, and any further analysis is likely to have few patients to make meaningful conclusion. It will also have a significant impact on potential addressable population eligible for reimbursement (with consequences on commercial sustainability of life-saving therapies if patient pool is too small). The introduction of a formal credibility assessment tool (ICEMAN) may raise concerns regarding its interpretation and reliability. The subjective nature of assessing credibility could lead to inconsistencies or disagreements in the evaluation of subgroup findings, which may impact the overall assessment outcomes.
- III. ICER’s efforts to improve patient-voice in its determination are a step in the right direction, however they fall short of best-practices and ICER should make truly meaningful changes to include patient groups throughout the assessment process, including having relevant patients/advocacy group representatives in the disease areas being assessed as standing voting members of its assessment committees.¹⁵⁻¹⁷
- IV. Changes to the ICER VAF reflect a trend towards less consultation rather than improved consultation. ICER should have a more robust input session around proposed changes to its VAF that includes adequate time for feedback and engages relevant experts, health care decision makers, manufacturers, payers, and patients.

We appreciate ICER's consideration of our proposed changes and welcome the opportunity to collaborate towards a more robust and balanced understanding of the value of the innovations that will ultimately result in a better health-care system and most importantly improved patients' lives.

References

1. Garrison, Louis P., et al. “Good Research Practices for Measuring Drug Costs in Cost-Effectiveness Analyses: A Societal Perspective: The ISPOR Drug Cost Task Force Report—Part II.” *Value in Health*, vol. 13, no. 1, Jan. 2010, pp. 8–13, <https://doi.org/10.1111/j.1524-4733.2009.00660.x>. Accessed 17 May 2020.
2. Julia Thornton Snider, PhD, et al. “The Option Value of Innovative Treatments for Non–Small Cell Lung Cancer and Renal Cell Carcinoma.” *www.ajmc.com*, vol. 23, no. 10, 25 Oct. 2017, www.ajmc.com/view/the-option-value-of-innovative-treatments-for-nonsmall-cell-lung-cancer-and-renal-cell-carcinoma. Accessed 30 June 2023.
3. Lakdawalla, Darius, et al. “The Insurance Value of Medical Innovation.” *Journal of Public Economics*, vol. 145, Jan. 2017, pp. 94–102, <https://doi.org/10.1016/j.jpubeco.2016.11.012>. Accessed 14 May 2020.
4. Lakdawalla, Darius N., et al. “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, Feb. 2018, pp. 131–139, <https://doi.org/10.1016/j.jval.2017.12.007>.
5. ---. “How Cancer Patients Value Hope and the Implications for Cost-Effectiveness Assessments of High-Cost Cancer Therapies.” *Health Affairs*, vol. 31, no. 4, Apr. 2012, pp. 676–682, <https://doi.org/10.1377/hlthaff.2011.1300>. Accessed 11 May 2020.
6. Li, Meng, et al. “Do Cancer Treatments Have Option Value? Real-World Evidence from Metastatic Melanoma.” *Health Economics*, vol. 28, no. 7, 24 June 2019, pp. 855–867, <https://doi.org/10.1002/hec.3899>. Accessed 11 Apr. 2022.
7. ---. “How Does Option Value Affect the Potential Cost-Effectiveness of a Treatment? The Case of Ipilimumab for Metastatic Melanoma.” *Value in Health*, vol. 22, no. 7, July 2019, pp. 777–784, <https://doi.org/10.1016/j.jval.2019.02.002>. Accessed 11 May 2022.
8. Ma, Siyu, et al. “Measuring “Fearonomic Effects” in Valuing Therapies: An Application to COVID-19 in China.” *Value in Health*, vol. 23, no. 11, July 2020, <https://doi.org/10.1016/j.jval.2020.06.002>. Accessed 20 Aug. 2020.
9. Reed, Shelby D., et al. “Quantifying Value of Hope.” *Value in Health*, vol. 24, no. 10, Oct. 2021, pp. 1511–1519, <https://doi.org/10.1016/j.jval.2021.04.1284>. Accessed 18 Mar. 2022.
10. Shafrin, Jason, et al. “Measuring the Value Healthy Individuals Place on Generous Insurance Coverage of Severe Diseases: A Stated Preference Survey of Adults Diagnosed with and without Lung Cancer.” *Value in Health*, vol. 24, no. 6, June 2021, pp. 855–861, <https://doi.org/10.1016/j.jval.2020.06.021>. Accessed 22 Mar. 2022.
11. ---. “Patient versus Physician Valuation of Durable Survival Gains: Implications for Value Framework Assessments.” *Value in Health*, vol. 20, no. 2, Feb. 2017, pp. 217–223, <https://doi.org/10.1016/j.jval.2016.11.028>. Accessed 30 Jan. 2020.
12. Wong, William, et al. “Real-World Evidence for Option Value in Metastatic Melanoma.” *Journal Managed Care Specialty Pharmaceuticals*, vol. 27, no. 11, 1 Nov. 2021, pp. 1546–1555, <https://doi.org/10.18553/jmcp.2021.21192>. Accessed 30 June 2023.
13. Garrison, Louis P., et al. “Augmenting Cost-Effectiveness Analysis for Uncertainty: The Implications for Value Assessment—Rationale and Empirical Support.” *Journal of Managed Care & Specialty Pharmacy*, vol. 26, no. 4, Apr. 2020, pp. 400–406, <https://doi.org/10.18553/jmcp.2020.26.4.400>. Accessed 28 Jan. 2023.
14. Lakdawalla, Darius N., and Charles E. Phelps. “Health Technology Assessment with Diminishing Returns to Health: The Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Approach.” *Value in Health*, vol. 24, no. 2, Feb. 2021, pp. 244–249, <https://doi.org/10.1016/j.jval.2020.10.003>. Accessed 20 Aug. 2022.
15. National Health Council. “The National Health Council Rubric to Capture the Patient Voice: A Guide to Incorporating the Patient Voice into the Health Ecosystem. .” *National Health Council.*, July 2019, www.nationalhealthcouncil.org/Patient-Engagement-Rubric.
16. Peretto, Eleanor M., et al. “Value to Whom? The Patient Voice in the Value Discussion.” *Value in Health*, vol. 20, no. 2, Feb. 2017, pp. 286–291, <https://doi.org/10.1016/j.jval.2016.11.014>. Accessed 2 Feb. 2020.

17. University of Maryland, School of Pharmacy. "Patient-Driven Values in Healthcare Evaluation (PAVE)." www.pharmacy.umaryland.edu, 28 June 2023, www.pharmacy.umaryland.edu/programs/patient-driven-values-healthcare-evaluation-pave/. Accessed 30 June 2023.

June 30, 2023

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
<via email>

RE: Proposed Changes to 2023 Value Assessment Framework

The National Pharmaceutical Council (NPC) appreciates the opportunity to submit comments on ICER’s proposed changes to its value assessment framework (VAF).

NPC is a health policy research organization dedicated to the advancement of good evidence and science and to fostering an environment in the US that supports medical innovation. We have rich experience conducting research and disseminating information about the critical issues of evidence, innovation, and the value of medicines for patients. Our research helps inform important healthcare policy debates and supports the achievement of the best patient outcomes in the most efficient way possible.

NPC’s recommendations focus on the shortcomings of ICER’s proposed changes in terms of transparency, credibility, and methodological rigor:

- I. ICER’s assessments should rely on scientifically supported methods and align with best practices for value assessment.**
- II. ICER proposes multiple changes intended to tackle pervasive problems in the healthcare system, including accounting for health equity, productivity, and patient engagement. Significant improvements are needed to address these problems in reliable, appropriate, and patient-focused value assessments.**
- III. ICER is progressively eroding the transparency and rigor of its assessments, procedures, and interactions with stakeholders.**

I. ICER’s assessments should rely on scientifically supported methods and align with best practices for value assessment.

ICER’s shared savings scenarios should not be used as the basis for ICER’s health benefit price benchmarks (HBPBs); these scenarios are not supported by economic science or empirical evidence and can incentivize the use of less effective treatments.

ICER’s cost offset cap (\$150,000) and shared savings allocations (50% of cost offsets allowed) are not supported by any scientific research or empirical evidence. One of the many arguments that ICER has put forth for these scenarios is that savings should be “shared” by manufacturers with insurance plans. These trade-offs are the subject of negotiations between payers and manufacturers, not 3rd party value assessments. Furthermore, there is a strong consensus in the literature that US manufacturers receive a small percentage of the total social value arising from new drugs.^{1,2,3,4}

As acknowledged by ICER in a prior technical brief, the introduction of SSTs may often result in real-world cost offsets that far exceed \$150K per year, which include recurring patient treatment burdens and health system monitoring costs often missing from ICER assessments.⁵ In such cases, ICER’s application of its cost offset cap will result in value-based price determinations that are artificially and arbitrarily low and do not reflect the full value of the assessed treatments, biasing their HBPBs. ICER

states it may further elect to apply shared savings analyses to determine HBPs not only for SSTs, but also for any “*other treatments with relevant and substantial potential cost-offsets.*”⁶ By purposefully and artificially underestimating treatment value for SSTs or other treatments ICER promotes use of inefficient and expensive standards of care, further entrenching inefficiencies in healthcare provision.

ICER should not lower its cost-effectiveness thresholds, as doing so is not supported by the literature and could have severe downstream implications for patient access.

ICER discusses adjusting its cost-effectiveness thresholds in three distinct contexts: 1) application of an opportunity cost scenario; 2) the potential to shift its HBPB range to \$50,000 to \$100,000 per QALY in the future; 3) the potential to use a lower cost-effectiveness threshold in “highly unusual” situations.

First, ICER appeals to a flawed opportunity cost rationale, suggesting a top threshold of \$104K/QALY. However, ICER’s justification to support such an analysis derives from a single simulation study⁷ which relies on a myriad of unvalidated assumptions and narrowly selected methods for estimating cost-effectiveness thresholds.⁸ Moreover, this estimate is based on increases in total healthcare costs. This has no validity since this effectively assumes that drugs account for all increases in total healthcare spending. In contrast, prescription drugs account for less than 20% of spending and the multi-year downward trend in pharmaceutical net prices demonstrates that drug prices are not driving premium increases^{9,10} rather, health insurance premiums are increasing for many reasons, including the aging US population, the increasing prevalence of chronic disease, and cost growth in other forms of care. In a 2022 report, the Congressional Budget Office wrote “*The main reason for the growth of per-person spending by commercial insurers—and for the difference from the growth of per-person spending by Medicare FFS—has been rapid increases in the prices that commercial insurers pay for hospitals’ and physicians’ services.*”¹¹ Furthermore, as ICER noted in its most recent Policy Leadership Forum publication, markups charged to payers by hospitals when clinicians administer drugs in the hospital setting have been found to be as high as 200-300% of the base price of the drug.

ICER’s myopic, cost effectiveness-driven approach sets HBPs that are unjustified and unreasonably punish drug interventions – and by extension patients - for insurance market failures, inefficient health care services, and demographic changes. This underscores a disconnect between ICER’s methodological intention and its actual application: ICER aims to account for health care marketplace distortions, but solely penalizes emerging prescription drugs for these issues in their value assessments.

Second, ICER states that it will pursue further discussion with academic experts and stakeholders to consider whether the HBPB range should be shifted to \$50,000 to \$100,000 per quality-adjusted life-year (QALY). These lower cost-effectiveness ranges are substantially out of step with the literature on US willingness to pay for improved health. Application of these thresholds would be inappropriate and hold severe implications for innovation. A recent analysis found that authors of cost-effectiveness analyses increasingly cite \$100,000 to \$150,000 as appropriate thresholds, with cancer-related cost-effectiveness analyses referencing even higher thresholds.¹² Thresholds, where used, are known to vary by disease state and certainly by severity, resulting in a wide range of appropriate values which ICER does not acknowledge or incorporate. More broadly, applying threshold-based reporting, recommendations and decision-making can lead to lack of patient centric and clinically nuanced care.

Third, ICER states “*In highly unusual situations such as pandemics, in which there is an exceptionally large magnitude and urgency regarding the use of new health care interventions, ICER may consider using a lower cost-effectiveness threshold to provide additional accommodation between pricing to value and affordability...ICER will highlight these analyses in the Draft Report and provide justification for their planned inclusion within ICER’s HBPB range in Final Reports.*” NPC is very concerned that

ICER's inclusion of this language creates the potential for ICER to subjectively use ever-lower cost-effectiveness thresholds in future assessments, and to arbitrarily make unjustified methodologic changes on a whim without transparency or stakeholder engagement.

ICER's attempt to make itself useful to CMS's Medicare Drug Price Negotiation Program (DPNP) is fraught with data gaps, uncertainty, and methodological limitations.

ICER proposes calculating new cost-effectiveness analyses related to the potential effects of the DPNP. However, significant uncertainty and gaps in data negate the utility of such analyses. ICER examines new treatments, many of which do not even have a list price, so ICER will have to make a series of ill-informed assumptions regarding future CMS spending on novel treatments and treatment prices many years after their value assessments.

ICER's decision to speculatively estimate whether and how emerging products will be subject to the DPNP 9 to 13 years in the future underscores ICER's inconsistent approach to evidence-based analysis. ICER is willing to undertake deeply speculative analyses that will be of no use to CMS, yet ICER refuses to undertake lifecycle dynamic pricing analyses incorporating the impact of branded and generic competition for which there is ample evidence.¹³ This remains a gap in the VAF.

ICER should incorporate additional dimensions of value not fewer; ICER's proposed changes will further narrow the definition of value in ICER assessments.

NPC has repeatedly called for ICER to better include patient-centered value elements in its assessments, both quantitative and qualitative. ICER states that "*methodological issues related to double counting and the inability to measure related opportunity costs present a strong argument to keep these dimensions as qualitative considerations at this time.*" However, this assertion ignores noteworthy progress that has been made in identifying rigorous theoretical and mathematical foundations for additional dimensions of value including insurance value, real option value, value of hope, and value of knowing.^{14,15,16,17} Moreover, incorporating these dimensions aligns with recommendations from patient groups, researchers, and health economists to advance more comprehensive and patient-focused assessments of treatment value.

ICER's justification for excluding broader value evidence due to a lack of evidence demonstrates its inconsistency and contradictory approach to performing evidence-based analyses. We are concerned that ICER is progressively including fewer dimensions of value in its appraisal committee deliberations, now including only votes on unmet need, caregiver quality of life, and equity considerations. Previously these votes incorporated factors of importance to patients such as complexity, lifetime impact, and mechanism of action. Not only is ICER failing to include these important value elements quantitatively; ICER is limiting even their meaningful qualitative inclusion.

ICER should incorporate sub-group analyses that are appropriate for a given disease and treatment.

NPC encourages ICER's interest in sub-group analyses but is concerned about the process by which these sub-groups will be defined and implemented. Sub-group analyses are clearly important to prescribers and plans regarding choices about appropriate care and benefit design. However, relevant sub-groups will vary substantially by disease state and specific indication for which reimbursement is sought. In addition, sub-groups not pre-specified in clinical trials may not have adequate sample size to make firm conclusions and urge caution and clarity when assessing the impact of sub-group analyses on HBPBs. We recommend that ICER include patients, manufacturers, and payers in the discussions leading to sub-group definitions incorporated into scoping documents and assessment protocols. We further encourage ICER to clarify the role of these sub-groups in estimated HBPBs.

ICER should include a true societal perspective as a co-base case in accordance with best practices for health technology assessment (HTA).

Despite repeated stakeholder calls to increase its use of the societal perspective, including past guidance from NPC, ICER will not promote the societal perspective to a co-base case for all assessment. This decision is out of step with other HTA bodies, Second Panel recommendations,¹⁸ and feedback from stakeholders representing patients, industry, and academia.¹⁹ And, as employers and their employees are the ultimate payer for most non-elderly healthcare in the US, we further call on ICER to greatly expand the role of patient and caregiver perspectives on treatment value. Incorporating diverse employer perspectives in assessments will help achieve this goal.

II. ICER proposes multiple changes to its framework that are intended to tackle pervasive issues in value assessment, including accounting for health equity, productivity, and patient engagement. Additional improvements are needed to advance reliable, appropriate, and patient-focused assessments.

NPC appreciates ICER's recognition that productivity is an essential component of treatment value. Accounting for productivity when calculating cost-effectiveness using a modified societal perspective, even when data are unavailable, will lead to more comprehensive assessments.

ICER proposes to include “non-zero” productivity data when using a modified societal perspective. NPC appreciates ICER’s acknowledgement of the importance of productivity data and encourages ICER to expand this acknowledgement to recognizing the importance of a co-base case for the societal perspective and the inclusion of other patient-centered value elements.

NPC is concerned about the validity and implementation of ICER’s proposed indirect approach to estimating the potential impact of productivity. As a first step, we encourage ICER to conduct straightforward evaluations of the large number of real-world productivity studies in the US where productivity data appear to be lacking. More importantly, best practices have emerged to better account for productivity gains due to life extension, delayed disease progression, and improved physical functioning.^{20,21} In addition, greater clarity is needed around how this methodology will be applied in cases where relevant productivity data are available.²² Clarity on how ICER will decide which estimates to use is needed.

Improving clinical trial diversity is imperative. However, NPC cautions that ICER should not be the arbiter on this issue – improving and assessing clinical trial diversity is a multi-stakeholder collaborative effort.

Advancing equity in health care and value assessment is critical. However, ICER’s rationale for choosing to opine on clinical trial diversity is unstated. Will this be incorporated into ICER's HBPs; will comparator treatments also be subject to this evaluation? Ultimately, the proposal to incorporate new ICER-developed methods for rating clinical trials diversity is premature and subject to many data limitations identified by ICER itself in its health equity white paper, such as dated and imprecise definitions of race and ethnicity categories and lack of reliable disease-specific prevalence estimates for some racial and ethnic groups. Registrational trials are necessarily multi-national with designs driven by clinical, ethical, and regulatory concerns, not dictates of value assessment. Importantly, the FDA has initiated numerous efforts to improve clinical trial diversity and is in a better position to assess and evaluate progress than is ICER.²³

ICER is proposing to improve its approach to patient engagement, but additional steps must be taken to ensure these efforts will lead to more patient-focused inputs being incorporated into ICER's analyses and results vs. being a simple box-checking exercise.

ICER proposes multiple changes to its Patient Engagement Program, including honoraria for patient representatives to help address financial barriers that may hinder participation and convening a Patient Counsel to advise and strengthen ICER's current Patient Engagement Program. ICER must take steps to empower the Patient Counsel to independently evaluate whether these changes result in more meaningful and patient-focused assessments and results.

III. ICER is progressively eroding the transparency and rigor of its assessments, procedures, and interactions with stakeholders, ICER needs to adopt transparent review and assessment processes and implement a multi-stakeholder engagement approach.

NPC is deeply concerned that ICER is preparing to change its methods on a whim without transparency or stakeholder input. As noted, ICER states it "*may identify additional analyses within an assessment that are of relevance to policymaking such as shared-savings analyses. In such situations, ICER will highlight these analyses in the Draft Report and provide justification for their planned inclusion within ICER's HBPB range in Final Reports.*" This provides an opening for ICER to change the methods on the fly during any report. This is not a transparent, credible, stakeholder-informed approach.

In the simple process of describing these proposed updates to the VAF, ICER falls short of scientific norms. Any updates to the VAF should begin with a stated purpose for the update and include possible impact on HBPBs to allow stakeholders to make informed decisions. Further, with these proposals, ICER has shown its willingness to create in-house "methods" and implement them without scientific support (shared savings, trial diversity, e.g.) when it suits unstated aims and ignores scientific advancements developed elsewhere (broader value measures value, e.g.) when those run counter. ICER further notes that its topic selection and stakeholder engagement processes "*will be updated on an ad hoc basis and will not follow the standard three-year update cycle that the ICER value assessment framework currently follows.*" Added to the ever-decreasing stakeholder input and restricted comment periods that further limit external comments, ICER's process is becoming stridently anti-stakeholder. We fear that this trend, coupled with a flawed VAF 'update', will further undermine patient-centered value assessment in the US.

We appreciate this opportunity to provide input on proposed changes to ICER's VAF. 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.

Sincerely,

John Michael O'Brien, PharmD, MPH
President & Chief Executive Officer
National Pharmaceutical Council

References

1. Hult KJ, Philipson TJ. The Value of Medical Innovation Versus Industry Rewards. *Value Health*. 2023 Mar;26(3):320-327. doi: 10.1016/j.jval.2022.12.001. Epub 2022 Dec 9.
2. Berdud M, Wallin-Bernhardsson N, Zamora B, Lindgren P, Towse A. The Allocation of the Economic Value of Second-Generation Antipsychotics Over the Product Life Cycle: The Case of Risperidone in Sweden and the United Kingdom. *Value Health*. 2023 Mar;26(3):328-335.
3. Refoios Camejo R, McGrath C, Miraldo M, Rutten F. Distribution of health-related social surplus in pharmaceuticals: an estimation of consumer and producer surplus in the management of high blood lipids and COPD. *Eur J Health Econ*. 2014 May;15(4):439-45. doi: 10.1007/s10198-013-0484-1. Epub 2013 May 3. Erratum in: *Eur J Health Econ*. 2014 May;15(4):447.
4. Lindgren P, Löfvendahl S, Brådvik G, Weiland O, Jönsson B. Value appropriation in hepatitis C. *Eur J Health Econ*. 2022 Aug;23(6):1059-1070. doi: 10.1007/s10198-021-01409-7. Epub 2021 Dec 2. PMID: 34855072; PMCID: PMC9304061. Jena AB, Philipson T. Cost-effectiveness as a price control. *Health Aff (Millwood)*. 2007 May-Jun;26(3):696-703.
5. Institute for Clinical and Economic Review. Value Assessment Methods and Pricing Recommendations for Potential Cures: A Technical Brief. August 6, 2019. <https://icer.org/wp-content/uploads/2020/10/Valuing-a-Cure-Technical-Brief.pdf>
6. ICER Proposes Updates to Value Assessment Framework Methods and Procedures. ICER. Accessed June 22, 2023. <https://icer.org/news-insights/press-releases/icer-proposes-updates-to-value-assessment-framework-methods-and-procedures/#:~:text=ICER%20is%20accepting%20public%20comment%20on%20these%20proposals>.
7. Vanness DJ, Lomas J, Ahn H. A health opportunity cost threshold for cost-effectiveness analysis in the United States. *Annals of internal medicine*. 2021;174(1):25-32.
- 8 Examples include the value of a statistical life (VSL) and willingness-to-pay (WTP).
8. IQVIA Institute. The Use of Medicines in the U.S. 2023: Usage and Spending Trends and Outlook to 2027. May 2, 2023. Available at: <https://www.iqvia.com/insights/the-iqvia-institute/reports/the-use-of-medicines-in-the-us-2023>
9. Janssen. The 2022 Janssen U.S. Pricing Transparency Brief. May 2023. Available at: https://transparencyreport.janssen.com/_document/2022-janssen-transparency-report-pdf?id=00000188-267e-d95e-abca-7e7e58750000
11. The Prices That Commercial Health Insurers and Medicare Pay for Hospitals' and Physicians' Services. Congressional Budget Office. <https://www.cbo.gov/publication/57422>
11. Neumann PJ, Kim DD. Cost-effectiveness Thresholds Used by Study Authors, 1990-2021. *JAMA*. 2023 Apr 18;329(15):1312-1314.
12. Cohen JT. The impact on cost-effectiveness of accounting for generic drug pricing: Four case studies. *Value in Health*. Published online November 2022. doi:<https://doi.org/10.1016/j.jval.2022.09.011>

-
13. Neumann PJ, Garrison LP, Willke RJ. The History and Future of the “ISPOR Value Flower”: Addressing Limitations of Conventional Cost-Effectiveness Analysis. *Value Health*. 2022 Apr.; 25(4):558-565.
14. dosReis S, Butler B, Caicedo J, Kennedy A, Hong YD, Zhang C, Slejko JF. Stakeholder-Engaged Derivation of Patient-Informed Value Elements. *Patient*. 2020;13(5):611-621.
15. Mattingly, T.J., Slejko JF, Onukwugha E, Perfetto EM, Kottlil S, Mullins CD. Value In Hepatitis C Virus Treatment: A Patient-Centered Cost-Effectiveness Analysis. *Pharmacoeconomics*. 2019;38(2):233-242.
16. Ma S, Olchanski N, Cohen JT, Ollendorf DA, Neumann PJ, Kim DD. The Impact of Broader Value Elements on Cost-Effectiveness Analysis: Two Case Studies. *Value Health*. 2022 Aug;25(8):1336-1343.
17. The Second Panel on Cost-Effectiveness in Health and Medicine. Recommendations on perspectives for the reference case. In: Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, eds. *Cost-Effectiveness in Health and Medicine*. 2nd ed. New York: Oxford University Press; 2017.
18. Institute for Clinical and Economic Review. Public comments on Methods Update: Value Assessment Framework 2020-2023. October 18, 2019. Available at: <https://icer.org/assessment/value-assessment-framework-2020/#timeline>
- 20 Basu A. Estimating costs and valuations of non-health benefits in cost-effectiveness analysis. In: Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, editors. *Cost-effectiveness in health and medicine*, 2nd edn. Oxford University Press, New York; 2017.
- 21 Jiao B, Basu A. Associating Health-Related Quality-of-Life Score with Time Uses to Inform Productivity Measures in Cost-Effectiveness Analysis. *Pharmacoeconomics*. 2023 Mar 6.
- 22 Basu A. Understanding Productivity Benefits and Related Future Research Needs in Cost-Effectiveness Analysis. *Value and Outcomes Spotlight*. July/Aug 2018. https://www.ispor.org/docs/default-source/publications/value-outcomes-spotlight/july-august-2018/ispor-vos-august-2018-heor-article-understanding-productivity.pdf?sfvrsn=88036c16_2
19. FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials. FDA. Published April 20, 2022. <https://www.fda.gov/news-events/press-announcements/fda-takes-important-steps-increase-racial-and-ethnic-diversity-clinical-trials>



June 30, 2023

Submitted electronically to publiccomments@icer.org

RE: ICER Proposed Updates to Value Assessment Framework

Otsuka America Pharmaceutical, Inc. (Otsuka) appreciates the opportunity to submit comments on the Institute for Clinical and Economic Review's (ICER's) proposed changes to its methods and processes for conducting value assessments.ⁱ

Otsuka and its affiliates oversee research and development and commercialization activities for innovative products in North America. At Otsuka, our driving philosophy is to defy limitation, so others can too. We seek to serve those with unmet medical needs in three important treatment areas: nephrology, central nervous system, and digital therapeutics. Otsuka is proud to be at the forefront of the research and development of new therapies designed to help patients with Alzheimer's disease, mental illness, and chronic kidney disease. We respect the value within every mind—whether it's a grand idea that changes the world, a simple human connection that changes someone's life, or something in between.

Otsuka offers comments on various elements of the Value Assessment Framework, including the new "Clinical Trial Diversity" subsection, subpopulation analyses, long-term cost effectiveness evaluation methods, and stakeholder engagement, which are described in more detail below.

A. Comparative Clinical Effectiveness (2)

Otsuka supports ICER's efforts to emphasize and evaluate clinical trial diversity and believes this is an important step toward equitable care. We share ICER's concern that ethnic minorities, who experience the highest disease burden, are often underrepresented in clinical trials. Among trials for new molecular entities and biologics approved in 2020, just 11% of study participants were Hispanic, 8% were Black and only 6% were Asian.ⁱⁱ We do, however, have several comments on the proposed diversity ratings and subpopulation analysis (as described in Sections 2.1 and 2.2 of the proposal) that we respectfully ask ICER to consider before finalizing the framework:

- a) ***Reconsider the exclusion of certain minority populations:*** The proposed diversity rating framework overlooks Native American, Alaskan Native, and Native Hawaiian or Pacific Islander populations. Although we understand ICER's rationale for excluding groups under 5%—the limited availability of prevalence estimates and recruitment challenge—we are concerned that this approach may, unfortunately, further perpetuate disparities. We encourage ICER to develop guidance on how these underrepresented race groups can be incorporated into

the diversity rating scale to mitigate any unintended biases when evaluating therapies for these underrepresented patient groups. One potential solution is to revisit the race/ethnic categories in light of the US Census categorization.ⁱⁱⁱ In addition, we recommend considering socioeconomic and cultural factors that may also impact health equity.

- b) ***Distinguish among Asian populations:*** We encourage ICER to distinguish among different Asian populations when analyzing disease prevalence to the extent possible, as some disease states may be higher among Asians from certain backgrounds.
- c) ***Evaluate data collection methods:*** Data collection methods can affect the accuracy and reliability of the data, potentially leading to biased or incomplete representation of racial and ethnic groups. ICER should analyze how race/ethnicity data were collected in different trials, including whether participants self-reported or if other approaches were used.
- d) ***Support planning and recruitment for diversity in clinical trials:*** We encourage ICER to review and incorporate insights from the recent FDA guidance and other recent publications on clinical trial diversity planning.^{iv} This guidance provides valuable insights into ensuring participant diversity and inclusivity in clinical trials. ICER should consider tracking recruitment methods, which promotes increased diversity, in addition to tracking outcomes.
- e) ***Clarify statements about data availability:*** We request that ICER elaborate on the statement, "[I]f these data are not published and not provided to ICER, ICER will focus on the diversity of the entire trial population." Further clarification is necessary to ensure transparency and consistency in the assessment process when the preferred diversity data are not available.
- f) ***Explain Participant to Disease Prevalent Ratio (PDRR):*** ICER has not specified how it defines race group in its PDRR. It is not clear if self-identified race is the only consideration or if ancestry-based race groups are also included. A 2021 New England Journal of Medicine report discussed the complex link between race and ancestry and how ancestry may improve clinical interventions,^v and we encourage ICER to provide more guidance on this topic.
- g) ***Provide additional guidance on how gender and race are factored into PDRR when a disease is concentrated among certain groups:*** ICER does not consider gender in its evaluation of sex-specific conditions, such as breast cancer, which is far more prevalent in females. It also does not explain how it factors race into PDRR for conditions that are highly prevalent or driven in a specific racial group. For example, how does ICER assign a diversity rating for melanoma, which is 20 times more prevalent in White than Black populations? Are weighting methods considered for such scenarios? Please provide more guidance on this topic.
- h) ***Reconsider automatically excluding all multinational trials from diversity ratings:*** Rather than automatically excluding multinational trials, we encourage ICER to consider developing diversity ratings for studies conducted in countries where there is potentially comparable diversity to the U.S., such as the United Kingdom, France, and Germany. Ignoring these trials could result in missed opportunities to understand treatment effects across diverse populations.

- i) **Clarify how a priori subpopulations are identified:** In the proposed changes, specifically in 2.2 Subpopulation Analyses, ICER should clarify whether they plan to include the same *a priori* list of subpopulations of interest for each disease state they examine, or if reviews involving the same disease state may have different *a priori* subpopulations, based on other factors like data source, clinical trial populations, and availability.
- j) **Expand net health benefit guidelines:** We ask ICER to expand its guidelines on the net health benefit (NHB) calculation and its inclusion as a key output from health economic assessments.

B. Long-Term Cost Effectiveness (3)

1. Modified Societal Perspective and Productivity Inputs (3.1)

Otsuka believes the introduction of new methods to incorporate productivity impacts for patients and caregivers within a modified societal perspective is a step in the right direction. Our pipeline includes treatments for psychological conditions which have significant impacts on quality of life and carry societal burdens. Recognizing the broader value that pharmaceutical interventions can bring beyond only physical health outcomes is important. However, we urge ICER to consider the challenges in quantifying and valuing productivity inputs, especially when direct data are lacking. Collaboration with stakeholders, including patient advocacy groups and industry experts, can help ensure a robust and transparent approach in determining these inputs. We recommend continued refinement of these methods to capture the full range of patient and caregiver value, acknowledging the diversity of perspectives in the community. Please consider the following comments:

- a) **Consider potential wage and age adjustments:** ICER proposed the use of the modified societal perspective, with the same wage rates for all patients and informal caregivers. ICER noted that societal costs should be included using the human capital approach, assuming full or nearly full employment, but we believe this is often unrealistic, with U.S. labor force participation rate at 62.6%.^{vi} In addition, the work of affected individuals can often be replaced by other eligible workers hired during the period when the patient is unable to work.

Further, without age-adjustment, an analysis of societal costs may not accurately reflect economic contributions due to differences in labor market participation rates, skills, and earning potential between younger and older individuals. This could lead to an underestimation of younger individuals' economic contributions or overestimation of older individuals' economic contributions. One possible solution is the use of age-adjusted salaries to account for unequal employment rates. This has been implemented in Denmark's Health Technology Assessment guidelines^{vii}, which consider factors such as age and sex to provide more comprehensive insight into the costs and benefits of healthcare interventions. These adjustments enable decision-makers to better assess the value of interventions for subgroups.

- b) *Consider whether assumptions based on U.K. data are valid in the U.S.:* Otsuka is concerned that the U.K. data used to inform the assumptions about caregiver time may not necessarily be accurate in the U.S. context. While there may be some similarities between the two healthcare systems, differences in healthcare practices, cultural norms, and resource allocation may impact the relevance and generalizability of such values. A comparative analysis between U.K. and U.S. datasets, along with an evaluation of contextual factors, would provide a stronger foundation for making informed value assessments.

2. *Dynamic Pricing Scenario: Impact of Medicare Drug Price Negotiation on Cost-Effectiveness Scenarios (3.2)*

Otsuka appreciates the importance of cost-effectiveness scenarios that reflect the potential effects of the Inflation Reduction Act (IRA) drug price negotiation and understands the challenges of doing so, as the negotiation process itself is unclear at this time. We wonder, however, how ICER's current cost-effectiveness scenario will improve decision-making given that Congress included language within the IRA that prohibits use of the quality-adjusted life year (QALY) methodology in the negotiations. Any clarity regarding methods of assessing value in this section of the VAF would be helpful to industry.

We believe it is essential to incorporate realistic scenarios that capture the dynamic nature of the pharmaceutical pricing landscape. We encourage ICER to ensure that these scenarios accurately account for the complexities and potential trade-offs associated with drug pricing policies. A comprehensive analysis should consider the impact on innovation, patient access, and the sustainability of the healthcare ecosystem to provide a more balanced assessment.

3. *Other Changes: Incorporating Real-World Evidence (3.5)*

We appreciate ICER's willingness to evaluate real-world evidence (RWE) in value assessments, but the process by which ICER will include and grade this evidence remains unclear. Otsuka recommends that ICER clarify the types of RWE that will be evaluated (e.g., qualitative vs. quantitative, different study designs, etc.). ICER should also provide comprehensive guidance on its evaluation of RWE studies. Its proposed changes to its VAF do not address the growing role of RWE in health technology assessments (HTA). Clear and standardized criteria for assessing the quality, relevance, and reliability of RWE would promote consistency in evaluations and ensure that all relevant stakeholders can effectively contribute to the value assessment process.

C. Potential Other Benefits or Disadvantages and Contextual Considerations (4)

Otsuka agrees that the amended Likert-scale voting format will be clearer and more transparent with regard to weighting these factors during the assessment process, and we think the patient-focused question on unmet need is critically important. But we also encourage ICER to consider adding another question about whether the new treatment offers functional benefits for patients

would further assess the usefulness of the treatment to the patient population (e.g., “**Patients:** The treatment is likely to produce significant improvement in patients’ quality of life and/or ability to pursue their own education, work, and family life.”).

D. Stakeholder Engagement (A.3)

Otsuka applauds ICER’s efforts to improve and strengthen stakeholder engagement through changes to the Patient Engagement Program. Capturing patient experience and ensuring a diversity of voices is vitally important. We support the improvements to the *Share Your Story* form, small group patient and caregiver discussions, and compensation. We also request that you consider the following suggestions:

- a) ***Expand outreach to encourage more patients to share their stories:*** Patient representation is vital in value assessments, but limited access to the "Share Your Story" form may hinder inclusion of diverse voices and skew outcomes. We recommend ICER implement a multifaceted approach to widely disseminate the form, such as partnering with patient advocacy organizations, healthcare facilities, and social media platforms. Proactive outreach, including targeted communication campaigns, can help ensure equal opportunity for patients from diverse backgrounds to share their experiences and contribute to the assessment process.

- b) ***Focus on ensuring meaningful geographic and racial/ethnic diversity among the patient and caregiver participants:*** Achieving meaningful diversity in the small group feedback sessions is crucial to capture a range of perspectives and experiences that reflect the diverse populations impacted by the assessed interventions. Geographic and race/ethnic diversity are key aspects that need to be considered to avoid bias and ensure equitable representation. We encourage ICER to strive to achieve meaningful diversity in its small group feedback process. Clear criteria for participant selection should be established to ensure equitable representation. Necessary support, such as language translation services, should be provided to enable meaningful participation from individuals with diverse backgrounds.

* * * * *

Otsuka appreciates the opportunity to comment on the proposed changes to the value assessment framework. If you have any questions about these comments, please contact Heidi Waters, Senior Director Policy Research at Heidi.Waters@otsuka-us.com.

Sincerely,

Kaan Tunceli
Vice President, Global Value & Real World Evidence
Otsuka Pharmaceutical Development & Commercialization, Inc.

ⁱ ICER Proposes Updates to Value Assessment Framework Methods and Procedures, ICER (June 5, 2023), <https://icer.org/news-insights/press-releases/icer-proposes-updates-to-value-assessment-framework-methods-and-procedures/>; 2023 Value Assessment Framework: Proposed Changes, ICER (June 5, 2023), https://icer.org/wp-content/uploads/2023/06/Proposed-VAF-Changes-For-Public-Comment_For-Publication_06052023.pdf.

ⁱⁱ *Driving diversity and democratization within clinical trials*, STAT NEWS (Oct. 28, 2021), <https://www.statnews.com/sponsor/2021/10/28/driving-diversity-and-democratization-within-clinical-trials/>; U.S. Food & Drug Admin., *2020 Drug Trials Snapshots Summary Report*, (Feb. 2021), <https://www.fda.gov/media/145718/download>.

ⁱⁱⁱ Eric Jensen et al., *Measuring Racial and Ethnic Diversity for the 2020 Census*, U.S. Census Bureau (Aug. 4, 2021), <https://www.census.gov/newsroom/blogs/random-samplings/2021/08/measuring-racial-ethnic-diversity-2020-census.html>.

^{iv} U.S. Food & Drug Admin., *Clinical Trial Diversity* (Nov. 4, 2022), <https://www.fda.gov/consumers/minority-health-and-health-equity/clinical-trial-diversity>; Mark R. Cullen et al., *A framework for setting enrollment goals to ensure participant diversity in sponsored clinical trials in the United States*, 129 CONTEMPORARY CLINICAL TRIALS 107184 (June 2023), <https://www.sciencedirect.com/science/article/pii/S1551714423001076?via%3Dihub>.

^v Luisa Borrell et al., *Race and genetic ancestry in medicine—a time for reckoning with racism*, 384 NEW ENGLAND J. MED 474. (2021).

^{vi} Bureau of Labor Statistics, *The Employment Situation – May 2023*, USDL-23-1196 (June 2, 2023), <https://www.bls.gov/news.release/pdf/empisit.pdf>.

^{vii} <https://www.sst.dk/en/English>



Response to ICER's Proposed Updates to Value Assessment Framework Methods and Procedures (published June 5, 2023)

June 30, 2023

Dr. Steven D. Pearson

President

Institute for Clinical and Economic Review

14 Beacon Street, Suite 800

Boston, MA 02108

Dear Dr. Pearson,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the proposed changes to ICER's framework and processes for conducting value assessments. Pfizer's purpose is to deliver breakthroughs that change patients' lives. We focus our efforts in core areas where Pfizer is best positioned to advance innovative and much needed medicines and vaccines to enhance the health of patients, their families, caregivers, and society. With the ongoing discourse on measuring value and advancing value-based frameworks, Pfizer is committed to identifying solutions for a more effective, efficient, and equitable healthcare system in the US.

We appreciate ICER's efforts to update the Value Assessment Framework Methods and Procedures and the call for public comments. However, the comment period is extremely short, spanning only 20 business days. Given the importance of this work, we recommend ICER to expand the public comment period to July 30th, 2023, to allow stakeholders adequate time to reflect and respond on the proposed changes.

We address comments and recommendations within the following key areas:

A. Long-term Cost Effectiveness

- 1. Recommendation: ICER should incorporate generic pricing, instituted at the time of anticipated loss of exclusivity, into value assessments**
- 2. Recommendation: ICER should consider scenarios beyond the CMS ceiling price within cost-effectiveness analyses**

3. Recommendation: Cost-effectiveness thresholds should be at least maintained at \$100k - \$150k per QALY and not decreased while consideration for higher thresholds should be sought in certain circumstances

B. Potential Other Benefits or Disadvantages and Contextual Considerations

4. Recommendation: A quantitative approach to measure and incorporate value in a comprehensive and complete way such as Multi-criteria Decision Analysis (MCDA) should be implemented into value assessments

C. Comparative Clinical Effectiveness

5. Different evidence ratings should not be applied across different populations and subgroups

A. Long term Cost Effectiveness

1. Recommendation: ICER should incorporate generic pricing, instituted at the time of anticipated loss of exclusivity, into assessments

ICER has proposed to implement a dynamic pricing scenario for small molecule and biological products that are predominantly targeted to Medicare-eligible populations. However, ICER is not proposing to consider dynamic pricing beyond drugs targeted to the Medicare population. The omission of assumptions about genericization may misrepresent the cost-effectiveness analysis of the treatment under evaluation over the model's time horizon due to inaccurate pricing assumptions¹. ICER should seek to implement dynamic pricing consistently across situations where a significant price change at a specific point in time in the future would be anticipated.

2. Recommendation: ICER should consider scenarios beyond the CMS ceiling price within cost-effectiveness analysis

ICER has proposed to generate a dynamic pricing scenario for small molecule and biological products that are predominantly targeted to Medicare-eligible populations at the CMS-relevant ceiling price which will range from 40% - 75% of the previous non-federal average manufacturer

¹ Neumann P, Podolsky M, Basu A et al. Do Cost-Effectiveness Analyses Account for Drug Genericization? A Literature Review and Assessment of Implications. Value In Health. 2022; 25(1): 59-68.

price depending on how long the drug has been on the market. While the rationale for generating cost-effectiveness analysis specific for Medicare remains unclear given the Affordable Care Act prohibited Medicare from making decisions based on QALYs (and reiterated within IRA guidance²), should this be undertaken, a range or an estimate such as that suggested by Congressional Budget Office of 50%³ would be more informative than the maximum price.

3. Recommendation: Cost-effectiveness thresholds should be at least maintained at \$100k - \$150k per QALY and not decreased while consideration for higher thresholds should be sought in certain circumstances

ICER states that it will continue to explore whether “the Health Benefit Price Benchmark Price range should be shifted to \$50,000 to \$100,000/QALY or evLYG in order to better reflect the true opportunity costs experienced by many Americans.” In a working paper published in 2021, the Congressional Budget Office (CBO) used a value of statistical life year of \$388,000/life year and willingness-to-pay values of \$507,000/QALY, including sensitivity cases used values that were 50 percent higher and 50 percent lower.⁴ Employing lower thresholds effectively devalues life and suggests lower reimbursement for medications which would have detrimental effects on patient access to current and especially future medications.

Consistent with approaches used by HTA bodies such as the National Institute for Health and Care Excellence (NICE), we recommend that ICER consider alternative higher thresholds in instances of highly specialized technologies which offer particularly large health gains. Additionally, ICER has noted that in situations such as pandemics, they will consider using lower thresholds. From a methodological and ethical standpoint, this is not appropriate as the value of medications may be perceived as even greater in times of such high need therefore thresholds should at a minimum be maintained. Technically, the issue of budget constraints under such circumstances (e.g., a pandemic) are dealt with through other economic analyses such as budget impact analyses.

² DHSS. Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026, and Solicitation of Comments. [medicare-drug-price-negotiation-program-initial-guidance.pdf](https://www.cms.gov/medicare-drug-price-negotiation-program-initial-guidance.pdf) (cms.gov)

³ Congressional Budget Office. How CBO Estimated the Budgetary Impact of Key Prescription Drug Provisions in the 2022 Reconciliation Act. [58850-IRA-Drug-Provs.pdf](https://www.cbo.gov/publications/58850-IRA-Drug-Provs.pdf) (cbo.gov)

⁴ Adams, C. Herrnstadt, E. (2021). CBO’s Model of Drug Price Negotiations Under the Elijah E. Cummings Lower Drug Costs Now Act. Congressional Budget Office. Available at: <https://www.cbo.gov/system/files/2021-02/56905-Drug-Price-Negotiations.pdf>

B. Potential Other Benefits and Contextual Considerations

4. **Recommendation: A quantitative approach to measure and incorporate value in a comprehensive and complete way such as Multi-criteria Decision Analysis (MCDA) should be implemented into assessments**

It remains critical that ICER considers quantitative value assessment methodology which is non-QALY based given the very narrow focus of the QALY and discrimination against disabled⁵ and elderly populations making it an inappropriate measurement of healthcare within the US market. Although the “Equal Value of Life Years Gained” (evLYG) approach does not adjust for quality-of-life differences, it continues to discriminate against elderly patients as the methodology focuses on added life years of which the elderly potentially have less to gain and hence are instantly disadvantaged. The QALY approach and the evLYG approach produce results that differ only modestly.⁶

Research has highlighted that beyond clinical outcomes there are other important aspects that are of value to patients, caregivers, society, and the healthcare system⁷. ICER collects some of this information through the qualitative process and panel voting on “Potential Other Benefits or Disadvantages and Contextual Considerations.” ICER notes that the relative weight should be “left qualitative and subject to a public deliberative process.” Furthermore, ICER notes MCDA has been considered and rejected because ICER does not believe that the methods for weighting individual elements are robust enough to add to the reliability of value judgements.

MCDA is a widely recognized and accepted methodology for aggregating different dimensions of value enabling patient-centered value assessment^{8,9}. HTA are increasingly

⁵ National Council on Disability. (2021). “NCD letter to House Committees with concerns regarding H.R. 3.” Available at: <https://ncd.gov/publications/2021/ncd-letter-house-committees-concerns-regarding-hr-3>

⁶ Cohen J, Ollendorf D, Neumann P. Will ICER’s Response to Attacks on the QALY Quiet the Critics? <https://cevr.tuftsmedicalcenter.org/news/2018/will-icers-response-to-attacks-on-the-qaly-quiet-the-critics>

⁷ Lakdawalla D, Doshi J, Garrison et al. Defining Elements of value in health Care – a Health Economics Approach: an ISPOR Special Task Force Report. *Value in Health*. 2018; 21: 131-139.

⁸ National Pharmaceutical Council. *Multi-Criteria Decision Analysis: Can It Help Make Value Assessment More Patient Centered?* 2020. Washington, DC. Available at: <https://www.npcnow.org/sites/default/files/media/2020mcda-roundtable-nhc-npc-whitepaper-final.pdf>

⁹ Mendola ND, Oehrlein E, Perfetto EM, Westrich K, McQueen RB. Stakeholder perception of pharmaceutical value: A multicriteria decision analysis pilot case study for value assessment in the United States. *J Manag Care Spec Pharm*. 2022 Oct;28(10):1190-1196

adopting MCDA with ongoing initiatives in Europe¹⁰. MCDA can account for a range of perspectives and values, including health outcomes, patient-reported outcomes, and patient experience from the clinical, humanistic, and economic perspectives. MCDA can also account for health equity through these various perspectives and values. Importantly, MCDA also addresses many of the concerns of discrimination against disabled and elderly patients that are inherent in utility based QALY metrics further promoting health equity.

C. Comparative Clinical Effectiveness

5. Different evidence ratings should not be applied across different populations and subgroups

Advancing equity within healthcare needs to remain a top priority within the US healthcare system. While improving clinical trial diversity to reflect the patient population allows for more accurate treatment outcomes, trial diversity assessment needs to be part of a multi-stakeholder collaborative initiative in order to do so in a robust and valid way. Additionally, we do not believe that subgroup analyses should be given different evidence ratings within the review. This may lead to unintended consequences within clinical decision making. For example, a treatment might be cost-effective overall but concluded as not cost-effective in a particular subgroup; this has the potential to exacerbate existing healthcare inequities. Additionally, often the subgroups are not powered to show differences in clinical benefit unless this was pre-specified in the clinical trial design. It is our view that subgroup analysis should only be considered if a treatment is not deemed cost-effective but could have added benefits within a particular subgroup.

Sincerely,



Tatia Chay Woodward, MPH, MS
VP, Value & Evidence
Global Access & Value
Pfizer, Inc.
tatia.woodward@pfizer.com

¹⁰ Impact HTA. Improved Methods and Actionable Tools for Enhancing HTA. [Impact HTA | Health Technology Assessment | Work Package 7 \(impact-hta.eu\)](#)

June 30, 2023

VIA Electronic Submission – publiccomments@icer.org

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, Massachusetts 02108

Re: Feedback on 2023 Value Assessment Framework Proposed Changes

Dear Dr. Pearson,

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to respond to the Institute for Clinical and Economic Review’s (ICER) call for stakeholder input on its 2023 value assessment framework (VAF) proposed changes.¹ 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 \$1 trillion in the search for new treatments and cures, including \$91.1 billion in 2020 alone.

PhRMA is a long-standing supporter of the development of sound tools and evidence to support health care decision-making. This is reflected in our principles in support of Evidence-Based Medicine and Value Frameworks,² as well as our ongoing support for value assessment methods that capture patient differences and recognize uncertainty in value when new medicines are launched. Advancing better evidence and tools to support sound health care decision-making is a core element of our agenda.³

As with all value assessment organizations, it is important that ICER’s VAF reflects methodological best practices, takes a patient-centered approach, and transparently conveys for decision-makers the areas of controversy or uncertainty in its methods. We are concerned that the updates ICER is proposing to its framework move assertively in the other direction. On a number of issues, ICER has ignored a robust catalog of academic literature, innovative approaches to value assessment that address important methodological gaps, and deeply rooted concerns about serious issues, such as discrimination. Even in

¹ ICER. (2023). 2023 Value Assessment Framework Proposed Changes. Available at: https://icer.org/wp-content/uploads/2023/06/Proposed-VAF-Changes-For-Public-Comment_For-Publication_06052023.pdf

² PhRMA. (2016). Principles for Value Assessment Frameworks. Available at: <https://phrma.org/en/resource-center/Topics/Cost-and-Value/Principles-for-Value-Assessment-Frameworks>

³ PhRMA. Collaborating on Better Approaches to Value. Available at: <http://www.phrma.org/advocacy/the-value-collaborative>

instances where ICER has proposed new methods, it appears to have done so in a way that is highly selective and opportunistic. Rather than meaningfully evolve, the proposed updates to its VAF appear to reflect ICER's decision to entrench itself further in outmoded approaches to value assessment.

Particularly in view of ICER's proposed updates, we are also concerned about the process the organization is using to seek input, which is much more restrictive than for prior framework revisions and creates barriers to ICER obtaining meaningful input. The elimination of the open input period, significantly compressed comment timeline, and content limitations are inadequate for the solicitation, consideration, and thoughtful incorporation of feedback. Any VAF that purports to be fit for purpose for decision making must utilize better processes for receiving and responding to input.

ICER's approach to updating its framework appears similarly insulated from stakeholder consensus. We remain deeply troubled by ICER's continued reliance on cost effectiveness thresholds, its refusal to incorporate patient-centered value elements, and its failure to emphasize the societal perspective. As outlined below, it is clear that ICER's approach is fundamentally misaligned with the U.S' competitive and pluralistic market-based system, and when used in isolation cannot meet the needs of today's stakeholders or 21st-century science. Especially given the well-known flaws and discriminatory concerns, ICER's QALY-based estimates should not set the rule for pricing or policy decisions – if misused, it may result in dire consequences for patients (now and in the future).

And while we agree with ICER that patient engagement, clinical trial diversity, equity, and dynamic pricing are issues that should be considered in all value assessments, we have serious concerns with ICER's approaches to addressing these issues. Rather than make updates that only impact the margins of its VAF, we urge ICER to devote its resources to correcting its methods, including exploring entirely novel methods of value assessment.

While we recognize that ICER has requested that submitted comments are no longer than five-pages,⁴ we feel that this is a serious misstep that limits engagement with key stakeholders. As such, in addition to the bullets below, which summarize our key points to ICER, we are also including an addendum (Appendix A) to our comments that describe in more detail the several ways in which ICER can improve its framework to reduce the harm its methodology may have patients.

Our concerns and recommendations are summarized below.

- I. Actively explore and rely upon evidence-based alternative approaches to value assessment, rather than relying solely on CEA, rooted primarily in the QALY or similar metrics.** Given broad stakeholder concerns about the quality adjusted life year (and similar metrics), ICER should abandon use of the QALY in recognition of its significant flaws and the concerns of discrimination raised by key stakeholders. Furthermore, following significant and substantive work to develop alternative approaches to value assessment, ICER should give more serious consideration to such approaches that are appropriately tailored to the specific technology and decision context, including methodologies such as multi-criteria decision analysis (MCDA), even though no approach is perfect and complete.

⁴ ICER. (2023) ICER Proposes Updates to Value Assessment Framework Methods and Procedures. Available at: <https://icer.org/news-insights/press-releases/icer-proposes-updates-to-value-assessment-framework-methods-and-procedures/>

- II. Refrain from reliance on cost effectiveness thresholds; to the extent thresholds are used, refrain from reliance on thresholds that are artificially low.** ICER’s use of threshold-based CEA to set health benefit price benchmarks (HBPBs) is inappropriate given the patient-centric, decentralized U.S. health care system. ICER should stop relying on thresholds to set price benchmarks. We are also concerned that ICER strongly implies it may lower cost effectiveness thresholds in the future; Lower thresholds would further distort both resource allocation today and innovation incentives, reducing health attainment of future generations. Many thought leaders and institutions have relied upon and recommended use of a much *higher* threshold than what ICER currently uses to set HBPBs; there is no consensus that a lower threshold would be appropriate, as ICER claims.
- III. Adopt methodologies that recognize the impact of competition on the cost of medicines for all drug assessments.** Given the importance of accounting for significant pricing changes over the course of a drug’s lifecycle, it is encouraging that ICER is exploring a form of dynamic pricing in certain instances. However, ICER’s proposal falls significantly short of what is needed to adequately acknowledge the impact of competition on drug prices. This includes not just price reductions resulting from government prices setting (the focus of ICER’s proposal), but from a generic or biosimilar competitor late in the drug’s lifecycle, or brand-to-brand competition. These forms of competition also have a significant impact on the value of medicines over the course of their lifecycles.
- IV. Expand assessments (and importantly, results of assessments) to reflect all relevant benefits and impacts, including those identified based on clinical needs and preferences.** PhRMA is deeply disappointed that ICER has decided to continue ignoring the nearly universal call from stakeholders to *meaningfully* include the range of benefits offered by a medicine. Instead, ICER appears ready and willing to settle for an underestimation of the value of many treatments. ICER’s stated fear of “double counting” is not supported by evidence – rather it suggests a desire on ICER’s part to ensure that its HBPBs remain as artificially low as possible. As such, we urge ICER to reconsider its decision to only qualitatively incorporate certain elements of value.

Furthermore, as emphasized during the last VAF public comment period⁵ and from best practices and guidelines,⁶ inclusion of the societal perspective is critically important. Given the cross-stakeholder agreement on the importance of the societal perspective, it is perplexing, disappointing, and erroneous that ICER persists in only promoting the societal perspective as “co-equal” “on rare occasions.” PhRMA strongly recommends that ICER: 1) eliminate the criteria disease areas must meet in order for the societal perspective to be relied upon as a co-base case and 2) commit to promoting the societal perspective as a base case in all value assessments.

⁵ ICER. (2019). “Public Comments.” Available at: https://icer.org/wp-content/uploads/2020/10/ICER_2020_VAF_Open_Input_082119-2.pdf

⁶ Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, eds. (2017). The Second Panel on Cost-Effectiveness in Health and Medicine. Recommendations on perspectives for the reference case. In: *Cost-Effectiveness in Health and Medicine*. 2nd ed. New York: Oxford University Press.

- V. **Seek manufacturer feedback, embrace transparency, and issue value assessment results for subpopulation analysis.** While PhRMA appreciates the time spent in the VAF update to address acknowledgement and inclusion of subpopulations in its value assessments, we want to ensure these changes are meaningfully implemented into ICER’s framework. As such, ICER should authentically engage with key stakeholders to identify relevant subpopulations and justify included subpopulations for each analysis. Furthermore, other subpopulations beyond race/ethnicity, sex, and age should be included in assessments. To convey the impact of patient heterogeneity, ICER should issue evidence ratings and cost effectiveness findings based on these expanded subpopulations, particularly when they could facilitate improved access and coverage.
- VI. **Focus health equity efforts on improving shortcomings in core methods and processes rather than investing in a new and misguided effort to rate the diversity of clinical trials.** The lack of clinical trial diversity is a multi-faceted problem, and this is a misguided effort to hold one stakeholder accountable. Rating clinical trial diversity is both outside of ICER’s core expertise, and premature, given the FDA has not yet finalized its guidance, “Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Subgroups in Clinical Trials.” As such, ICER should first focus its efforts to address health equity issues within the currently used methods and process by:
- Avoiding the use of discriminatory metrics such as the QALY and other similar metrics;
 - Significantly improving mechanisms for engagement and input by patients and caregivers to ensure meaningful engagement with a diverse set of populations and viewpoints; and
 - Relying on real-world data to ensure disparities are reflected in key model inputs and outcomes, and, as a corollary, improving transparency to consistently acknowledge important gaps in evidence when they exist.
- VII. **Take a holistic perspective on value that reflects the full range of health care services and interventions and allocate a proportionate share of reviews to other health care services.** ICER should perform more non-pharmaceutical assessments to better reflect the full range of services and procedures that drive the majority of U.S. health spending. Unless ICER does so, it will fail to meet its previously stated goal of driving towards a “more effective, efficient, and just health care system.”⁷
- VIII. **Embrace a transparent, authentic process that fosters engagement of all parties.** While PhRMA is supportive of ICER’s planned steps towards an enhanced “Patient Engagement Program,” we have concerns based on its truncated approach to updating the VAF. To authentically and meaningfully engage patients, ICER must allow ample time to seek public comments and *meaningful* stakeholder engagement instead of quick ad hoc adjustments that

⁷ ICER. (2020). “2020-2023 Value Assessment Framework.” Available at: https://icer.org/wp-content/uploads/2020/10/ICER_2020_2023_VAF_102220.pdf

may have unintended consequences for patients.

We appreciate ICER's consideration of our recommendations. We provide more detail below as to specific concerns, as well as steps that ICER can and should take to address them in the attached addendum. We hope ICER will give full consideration to our concerns and the concerns laid out by other key stakeholders during this abbreviated comment period.

PhRMA and ICER have a mutual interest in the development of sound, patient-centered value assessments that support patient access and continued innovation. We appreciate ICER's engagement with our industry in the revision of its value framework and hope that you consider incorporating our feedback as the framework evolves.

Sincerely,

Lauren Neves, JD
Deputy Vice President, Policy & Research
PhRMA

Appendix A

PhRMA's detailed comments and recommendations for ICER are set forth below. We are concerned that if ICER does not address the issues set forth below there could be unintended harms to patients and continued biopharmaceutical progress. We urge ICER to allow more time for meaningful engagement and methodology improvements by revising their framework in accordance with the below recommendations.

I. ICER should actively explore and adopt evidence-based alternative approaches to value assessment, rather than relying solely on CEA, rooted primarily in the QALY.

ICER should abandon use of the QALY in recognition of its significant flaws and the concerns of discrimination raised by stakeholders.

A growing number of stakeholders and researchers are raising concern that QALY-based methods of value assessment are controversial and outmoded. From thought leaders in the field of health economics⁸ to patient advocates^{9,10} to policymakers, many have commented on the shortcomings of QALY-based cost effectiveness in general and the inappropriateness of their application in the U.S. health care system in particular. ICER itself has acknowledged the concerns expressed by stakeholders and the flaws in QALYs.¹¹

For these reasons, PhRMA is disappointed that, despite significant efforts toward developing its own alternative methods to value assessment, ICER will continue to rely on CEA alone as the core of its assessments and for setting its HBPBs.

In addition, the alternative metric developed by ICER, the evLYG, comes with its own significant flaws that render it unsuitable as an alternative.¹² While we appreciate ICER's implicit recognition of the need for alternatives to the QALY, using the evLYG in place of the QALY trades one set of flaws with another. While attempting to address discrimination due to discounting utilities for individuals with disabilities, ICER has created several other problems.

For example, when using the evLYG, medicines for conditions that do not reduce life expectancy, like a treatment for eczema or a cure for blindness, would demonstrate no value to the health care system. Additionally, the evLYG would value two medicines, one that reduces side effects and one that does not, as equal value. Neither the QALY nor the evLYG properly capture the value of a medicine to patients and people with disabilities. Americans should not be forced to choose between discrimination and capturing quality of life in value assessments. Such a conflict simply highlights the fact that traditional cost effectiveness assessments cannot possibly serve as an appropriate tool for setting price ranges.

⁸ Neumann P, Sanders G, et al. Cost Effectiveness in Health and Medicine, Second Edition. 2017.

⁹ American Association of People with Disabilities. (2021). "Reject Health Policies that Discriminate." Available at: <https://www.aapd.com/wp-content/uploads/2021/04/Reject-Health-Policies-that-Discriminate-1.pdf>

¹⁰ National Council on Disability. (2021). "NCD letter to House Committees with concerns regarding H.R. 3." Available at: <https://ncd.gov/publications/2021/ncd-letter-house-committees-concerns-regarding-hr-3>

¹¹ ICER. (2018). "The QALY: Rewarding the Care That Most Improves Patients' Lives." Available at: https://icer.org/wp-content/uploads/2020/12/QALY_evLYG_FINAL.pdf

¹² Paulden, M. (2020). Are the evLYG and HYT Approaches Viable Alternatives to the QALY? Presentation for Society for Medical Decision Making 2020 Virtual Meeting. YouTube. Retrieved June 29, 2023. Available at: <https://www.youtube.com/watch?v=MtNKI2VfTJw>

ICER should give more serious consideration to alternative approaches to value assessment, including those not rooted in traditional CEA.

PhRMA, as well as other stakeholders, have long urged ICER to explore alternative approaches to value assessment. PhRMA, as well as our sister organization, the PhRMA Foundation, have also supported individuals and organizations which have sought to address the well-known significant gaps in traditional value assessment.¹³ These individuals and organizations have made significant strides in this work, and have made themselves available to collaborate with ICER to incorporate their methods and processes into ICER's framework. For these reasons, it is particularly disappointing that ICER has (again) failed to sincerely explore alternative approaches to value assessment that are not rooted in CEA.

For example, ICER continues to reject multi-criteria decision analysis (MCDA) as too complicated and not robust enough. However, the University of Colorado, which has a strong working relationship with ICER, has been testing and applying novel methods for value assessment that encourage stakeholder engagement and promote value-based decision-making, including MCDA. As they note, "MCDA is particularly helpful in an area like coverage and reimbursement decision making, where the available alternatives are characterized by multiple, sometimes conflicting, criteria, some of which are judged objectively, some subjectively, and by multiple decision makers, each with his or her own views on a particular criterion's relative importance."¹⁴ Applying MCDA would allow individual users of ICER's reports to assign weight to different elements of value, and arrive at their own estimate of a treatment's worth, which is not currently the case in ICER's value assessments. Though MCDA is imperfect and still relatively novel, it is disappointing ICER has not taken steps to explore it more meaningfully.

If ICER persists in using CEA, after consultation with stakeholders, ICER should consider other new methods including generalized risk-adjusted cost effectiveness (GRACE),^{15,16} which flexibly accommodates adjustments for disease severity and diminishing returns to health. Though none of these novel approaches address every gap in value assessment methods, and each has flaws of its own, they at least attempt to better incorporate patient-centered values and prioritize equity and disease severity.

II. ICER's reliance on cost effectiveness thresholds is ill-suited for the U.S. health care system; furthermore, reliance on lower thresholds would be highly inappropriate.

As we have noted previously, PhRMA believes that use of cost effectiveness thresholds to make pricing or coverage decisions is fundamentally misaligned with personalized, patient-centered care. In countries where thresholds are used to determine prices or coverage, patients have less access to important treatments. For example, while 85 percent of all new medicines launched between 2012 and 2021 are reimbursed in the Medicare/Medicaid programs, only 48 percent of new medicines are reimbursed in the United Kingdom's public health care program.¹⁷ Similar to how a single QALY estimate cannot adequately capture the many aspects of value or the wide heterogeneity of patient preferences, the use of

¹³ PhRMA Foundation. (2023). Driving Progress in U.S. Value Assessment. Available at: https://www.phrmafoundation.org/wp-content/uploads/2023/01/Driving-Progress-in-U.S.-Value-Assessment_PhRMA-Foundation.pdf

¹⁴ The University of Colorado Pharmaceutical Value. (2019). Complimenting Coverage and Reimbursement Decisions With Multi-Criteria Decision Analysis. AJMC. Available at: <https://www.ajmc.com/view/complimenting-coverage-and-reimbursement-decisions-with-multicriteria-decision-analysis>

¹⁵ Lakdawalla DN, Phelps CE. (2021). Health Technology Assessment with Diminishing Returns to Health: The Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Approach. Value Health, 24(2):244-249. Available at: <https://pubmed.ncbi.nlm.nih.gov/33518031/>

¹⁶ Goldman D, Grogan J, Lakdawalla D, Liden B, Shafrin J, Than K, Trish E. (2023). Mitigating the Inflation Reduction Act's Adverse Impacts on the Prescription Drug Market. University of Southern California. Available at: <https://healthpolicy.usc.edu/research/mitigating-the-inflation-reduction-acts-potential-adverse-impacts-on-the-prescription-drug-market/>

¹⁷ PhRMA analysis of IQVIA MIDAS and country regulatory data, October 2022. Note: New active substances approved by FDA, EMA and/or PMDA and first launched in any country between January 1, 2012, and December 31, 2021. A medicine is considered publicly reimbursed in the United Kingdom if recommended by England's National Institute for Health and Care Excellence.

a 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 multi-faceted nature of our health care system and reaffirms the notion that a national-level threshold cannot be applied consistently across all end-users of ICER's reports.

While PhRMA continues to believe that reliance on cost effectiveness thresholds are antithetical to the movement towards personalized, patient-centered care in the U.S., we are concerned that ICER may be considering use of lower cost effectiveness thresholds as the basis for its HBPBs. ICER strongly implies that a threshold range of \$50,000-\$100,000/QALY would be appropriate for use in its value assessments, stating that it will continue to explore whether "the Health Benefit Price Benchmark Price range should be shifted to \$50,000 to \$100,000/QALY or evLYG in order to better reflect the true opportunity costs experienced by many Americans." ICER notes "important academic work" in willingness to pay methods (a statement it does not directly cite) as well as concerns over insurance premiums as the basis for its assertion that thresholds should be lowered.

PhRMA strongly disagrees with ICER that thresholds should be lower, given the impact that lower thresholds are likely to have on patient access to current and future medicines. Furthermore, ICER's statement that "important academic work" supports a lower threshold range ignores work by leading academics and U.S. government agencies, who have stated or signaled that the \$100,000-\$150,000/QALY is appropriate, or in some cases, too low. Research by Neumann and Kim find that US CEAs increasingly cite a range of \$100,000-\$150,000/QALY and thresholds for oncologic CEAs are higher than non-oncologic CEAs, suggesting that "diseases associated with greater mortality and morbidity warrant higher thresholds."¹⁸ In a working paper published in 2021, the Congressional Budget Office (CBO) used a value of statistical life year of \$388,000/life year and willingness-to-pay values of \$507,000/QALY, including sensitivity cases used values that were 50 percent higher and 50 percent lower.¹⁹

ICER's reference to cost effectiveness thresholds set in other countries is also misguided. Cost effectiveness thresholds such as those used the National Institute for Health and Care Excellence (NICE) were set many years ago and are not adjusted for inflation. Research has shown thresholds are declining in real terms and suggests they should be dynamically increased.²⁰

As stated above, PhRMA is fundamentally opposed to the use of thresholds to set price benchmarks. However, if ICER persists, it is critical that it report a broader range of price benchmarks that capture the societal perspective and other scenarios in ICER's value assessment reports. ICER's current approach implies there is a precision to its price benchmarks, which has been debunked by past research.²¹

III. ICER should adopt methodologies that recognize the impact of competition on the cost of medicines for all drug assessments.

¹⁸ Neumann PJ, Kim DD (2023). Cost-effectiveness Thresholds Used by Study Authors, 1990-2021. JAMA, 329(15):1312-1314. Available at: <https://jamanetwork.com/journals/jama/fullarticle/2803816>

¹⁹ Adams, C. Herrnstadt, E. (2021). CBO's Model of Drug Price Negotiations Under the Elijah E. Cummings Lower Drug Costs Now Act. Congressional Budget Office. Available at: <https://www.cbo.gov/system/files/2021-02/56905-Drug-Price-Negotiations.pdf>

²⁰ Low V, Macaulay R. (2022). Accounting for Inflation Within NICE Cost-Effectiveness Thresholds. Expert Rev Pharmacoecon Outcomes Res, 22(1):131-137. Available at: <https://pubmed.ncbi.nlm.nih.gov/33980118/>

²¹ Olchanski N, Cohen J, Neumann P. (2021). Unknown Unknowns – Uncertainty in Health Technology Assessment: A Case Study of PARP Inhibitors for Ovarian Cancer." Tufts Center for the Evaluation of Value and Risk in Health. Available at: <https://cevr.tuftsmedicalcenter.org/news/2021/unknown-unknowns>

PhRMA appreciates that ICER has finally acknowledged the importance of accounting for changes to drug prices at the end of a drug's lifecycle for certain drugs, specifically drugs likely to be subjected to price setting under drug pricing provisions of the Inflation Reduction Act (IRA). However, we are disappointed that ICER proposes to only apply dynamic pricing to drugs likely to be subject to Medicare price setting. Given robust evidence that many drugs face significant price competition both within and across classes of therapeutic options at some point in their life cycle, ICER should adopt dynamic pricing for all drug assessments.

Substantial price decreases for innovative medicines may result from a variety of factors, not only the market entry of generic and biosimilar competitors, but robust competition from other brand name drugs, as well as competition from the launch of generic and biosimilar competitors. For example, medication prices for innovative direct acting antivirals for Hepatitis C and PCSK9 inhibitors for lowering Cholesterol dropped by approximately 85 percent between 2015 and 2023, as a result of competition between brand drugs.²²

PhRMA does not believe ICER's rationale for failing to adopt dynamic pricing methodologies sooner or more broadly are well grounded. The fact that health technology assessment (HTA) agencies in other countries have not adopted dynamic pricing does not justify ICER rejection of a tool that can better capture the effects of market competition in the U.S. health system.

At a minimum, ICER should acknowledge the most predictable form of competition for a brand name drug, competition from a generic or biosimilar competitor late in the drug's lifecycle. Failure to account for genericization or a significant reduction in price at the end of a drug's lifecycle will lead to value assessments misrepresenting long-term opportunity costs. Recent research modeling the impact of accounting for generic drug pricing demonstrates that it could substantially reduce cost effectiveness ratios, and therefore is critical to improving the validity of value assessments.²³

Regarding drugs that are likely to be subject to price setting under the IRA, PhRMA recommends ICER monitor final maximum fair prices released by CMS and adjust its assumptions accordingly, rather than continuing to assume CMS will set prices at the statutory ceiling.

IV. ICER should expand assessments and results to reflect all relevant patient-centered outcomes based on clinical needs and preferences.

ICER should reconsider its proposal to only qualitatively incorporate a comprehensive, patient-centered set of value element into its value assessments.

PhRMA is disappointed that ICER will continue to ignore important elements of value, and instead will settle for an underestimation of the value of many treatments. The nearly universal call to include such elements meaningfully in value assessments has come from leading academics, the investor community, and most importantly, patients.²⁴ This call is rooted in an understanding that any value assessment that fails to incorporate of the full range of benefits and impacts of a treatment, including ICER's, is simply inaccurate.

Research has now shown the disparity between narrow, payer-centric value assessments and those that account for holistic, comprehensive elements of value. For example, recently presented research showed

²² PhRMA analysis of SSR Health, US Brand Rx Net Price Tool - Q1 2023. Percent change indicates difference between list price (WAC) at launch of first medicine in class and average sales-weighted net price in class through Q1 2023.

²³ Cohen J. (2023). The Impact on Cost-Effectiveness of Accounting for Generic Drug Pricing: Four Case Studies. Value Health, 26(3):344-350. Available at: <https://www.sciencedirect.com/science/article/abs/pii/S1098301522021908>

²⁴ ICER (2019). "Public Comments." Available at: https://icer.org/wp-content/uploads/2020/10/2020_VAF_Public_Comments_013120.pdf

that the value of biologics for the treatment of rheumatoid arthritis could, in some scenarios, nearly double when the value of risk reduction (also known as “insurance value”) was accounted for.²⁵

ICER’s fear of “double counting” is not supported by evidence – rather it suggests a desire on ICER’s part to ensure that its HBPBs remain as low as possible. As noted above, researchers have developed and tested methods to incorporate non-traditional value elements into value assessments, demonstrating that they have a meaningful impact on the HTA results. We urge ICER to work with these researchers and other stakeholders to re-examine ICER’s position on these other elements of value.

While PhRMA generally supports ICER’s proposal to include “non-zero inputs” for patient and caregiver productivity impacts, we have concerns about the methods and data proposed. For example, while ICER has proposed calculating “non-zero” productivity using the “human capital approach” that comes from a caveated 2016 manuscript,²⁶ ICER does not seemingly acknowledge the limitations with this approach which could prevent these methods from leading to meaningful change. We also strongly disagree with ICER’s decision to continue categorizing all other factors as “qualitative considerations,” while also limiting those factors to only include unmet need, caregiver quality of life, health equity considerations, and controversial, and un-validated “shortfall” measurements. This approach is inconsistent with meaningfully incorporating the patient perspective into assessments and out of step with the latest value assessment methodologic innovations.

ICER should consistently use the societal perspective as a co-base case in all value assessments.

During the last VAF public comment period, a wide range of stakeholders from leading health economists to patient advocates emphasized the importance of including societal benefits as part of a value assessment.²⁷ Best practices and guidelines from the fields of value assessment and cost effectiveness analysis also reinforce the importance of the societal perspective – for example, the widely cited recommendations from the Second Panel specify that reference case analyses should report results from a societal perspective in addition to a health care perspective.²⁸ As noted in the prior section with regard to elements of value, failure to present results based on the societal perspective prominently in ICER’s reports could lead to downwardly biased results of a value assessment. For example, a recent study found that inclusion of caregiver impacts – such as spillover costs like caregiver time and productivity loss, and spillover health outcomes – can have a significant effect on an assessment of an intervention’s value.²⁹

In response to stakeholder feedback, ICER committed to promoting the societal perspective as a co-base case when the relevant disease area or condition met certain criteria. For these reasons, many stakeholders were hopeful that following ICER’s last VAF update, ICER would promote the societal perspective as a co-based case consistently and frequently in its value assessments. Disappointingly, recent analysis showed that ICER included the societal perspective in less than one-third of its

²⁵ Goring S, Garrison LP, Jansen JP, Briggs, AH. (2021). Novel Elements of the Value Flower: Fake or Truly Novel. ISPOR. Available at: <https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-archives/issue/view/navigating-the-changing-heor-publishing-landscape/novel-elements-of-the-value-flower-fake-or-truly-novel>

²⁶ Basu A. Estimating costs and valuations of non-health benefits in cost-effectiveness analysis. Vol 2017: Oxford University Press New York; 2016.

²⁷ ICER. (2019). “Public Comments.” Available at: https://icer.org/wp-content/uploads/2020/10/ICER_2020_VAF_Open_Input_082119-2.pdf

²⁸ Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, eds. (2017). The Second Panel on Cost-Effectiveness in Health and Medicine. Recommendations on perspectives for the reference case. In: *Cost-Effectiveness in Health and Medicine*. 2nd ed. New York: Oxford University Press.

²⁹ Lin PJ, D’Cruz B, Leech AA, Neumann PJ, Sanon Aigbogun M, Oberdhan D, Lavelle TA. (2019). Family and Caregiver Spillover Effects in Cost-Utility Analyses of Alzheimer’s Disease Interventions. *Pharmacoeconomics*;37(4):597-608. DOI: 10.1007/s40273-019-00788-3. PMID: 30903567.

assessments, even excluding it for disease areas and conditions that met the criteria ICER itself set forth.³⁰

Given the cross-stakeholder agreement on the importance of the societal perspective, it is perplexing, and erroneous that ICER persists in only promoting the societal perspective as “co-equal” “on rare occasions.” PhRMA strongly recommends that ICER 1) eliminate the criteria disease areas must meet in order for the societal perspective to be relied upon as a co-base case and 2) commit to promoting the societal perspective as a co-base case in all value assessments. These steps are critical to ensuring that ICER is accurately estimating the full value of a treatment, and also critical to reassuring stakeholders that ICER is willing to align itself with methodological best practices and stakeholder consensus.

V. ICER should seek manufacturer feedback, embrace transparency, and issue value assessment results for subpopulation analysis.

PhRMA appreciates the time spent in ICER’s framework updates to address acknowledgement and inclusion of subpopulations in its value assessments. Health care is becoming increasingly personalized, and concerns about health equity necessitate more information and transparency about the impacts of treatments on different subpopulations.

We appreciate that ICER is proposing to make transparent its process for identifying relevant subpopulations and justifying which subpopulations it includes in its assessments. It is critical to engage with stakeholders, especially manufacturers, to identify relevant subpopulations prior to launching an assessment and to include a transparent justification for the inclusion or exclusion of a subpopulation in a specific assessment.

Although we agree that race/ethnicity, sex and age are important demographics to consider, we strongly urge ICER to not only include other subpopulations in its assessments (e.g., disability status, pediatric populations) but also clearly communicating limitations to any analysis. ICER should routinely issue evidence ratings and cost effectiveness findings based on these subpopulations to ensure the public has a clear understanding of the impact of treatments on subpopulations. Further, ICER should consider higher HBPBs for different subpopulations, if findings would potentially encourage better coverage and access to therapies for marginalized or vulnerable communities.

VI. ICER should refrain from rating the diversity of clinical trials and redouble its efforts to meaningfully address health equity in its methods and processes.

PhRMA is disappointed that ICER has declined to take meaningful steps to address health equity concerns in its framework. PhRMA agrees with ICER that improving clinical trial diversity is critically important to advancing health equity, and our industry, in collaboration with the Food and Drug Administration (FDA), has taken significant steps to address this issue. In 2020 we launched a comprehensive effort to increase diversity in clinical trials and address systemic barriers to participation by communities of color, seeking to help underrepresented patients be more involved in the research and development of potential life-saving medical treatments.³¹

Enhancing clinical trial diversity is a highly complex challenge that requires a community-based, multi-stakeholder approach. The remaining barriers reflect the reality that this is multi-faceted problem that extends beyond factors which are in control of any individual stakeholder. This attempt by ICER would

³⁰ Institute for Patient Access. (2023). “How Overlooking Societal Impact Undermines ICER’s Cost-Effectiveness Assessments.” Available at: https://instituteforpatientaccess.org/wp-content/uploads/2023/05/IfPA_ICER_SocietalPerspectivePaper_May-2023.pdf

³¹ PhRMA. (2020). Principles on Conduct of Clinical Trials Communication of Clinical Trial Results. Available at: <https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/PhRMAPrinciples-of-Clinical-Trials-FINAL.pdf>

hold pharmaceutical manufacturers responsible when they are only one stakeholder. PhRMA’s industry-wide principles on clinical trial diversity provide a foundation for collaboratively addressing the systemic barriers that can deter underserved communities from participating in clinical trials, and we invite ICER to be a part of this initiative.

However, rating clinical trial diversity is both outside of ICER’s core expertise, and premature, given the FDA has not yet finalized its guidance, “Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Subgroups in Clinical Trials.”³²

We recommend against ICER adding clinical trial diversity monitoring to its assessment framework, particularly given the other significant challenges that remain unaddressed, including a reliance on a model that is discriminatory and obscures the diverse needs of vulnerable populations. Instead, we recommend ICER take the following steps to address health equity within its methods and process:

- Avoid the use of discriminatory metrics such as the QALY and other similar metrics;
- Significantly improve mechanisms³³ for engagement and input by patients and caregivers to ensure meaningful engagement with a diverse set of populations and viewpoints; and
- Rely on real-world data to reflect disparities in key model inputs and outcomes, and, as a corollary, improve transparency to consistently acknowledge important gaps in evidence when they exist.

VII. ICER should take a holistic perspective on value that reflects the full range of health care services and interventions and allocate a proportionate share of reviews to other health care services and interventions.

Medicines are distinct from nearly any other health care service available to patients today. Investment in research and development provides value across the globe in ways that investment in other health care sectors, like building new hospitals and training additional physicians, are unable to achieve. The innovation lifecycle facilitates this global benefit through the use of generics and biosimilars while ensuring biopharmaceutical companies can maintain a sustainable business model in an area with a high degree of risk while continuing to invest in future innovations. Despite these unique characteristics, and the fact that spending on prescription medicines accounts for just 14 percent³⁴ of total health care costs in the U.S. while 44 percent³⁵ of all health spending in the private market goes to hospital services, ICER’s assessments remain primarily focused on medicines.

ICER’s myopic view on medicines is unfounded and undermines their stated mission of driving a “more effective, efficient, and just health care system.”³⁶ If ICER was truly dedicated to improving health care and guiding evidence-based resource allocation, assessments would take a holistic view of the health care system, not focus on a sector that accounts for such a small share of total health

³² U.S. Department of Health and Human Services. (2022). Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry. Available at: <https://aboutblaw.com/601>

³³ The Innovation and Value Initiative. (2020). Partnering with Patients: Principles and Commitments. Available at: https://www.thevalueinitiative.org/wp-content/uploads/2020/05/2020-IVI-Partnering-with-Patients-Brief_Final.pdf

³⁴ Roehrig, C., Turner, A. (2022). Projections of the Non-Retail Prescription Drug Share of National Health Expenditures. Altarum Institute. Available at: <https://altarum.org/sites/default/files/uploaded-publication-files/Projections%20of%20Non-Retail%20Drug%20Share%20of%20NHE%202022.pdf>

³⁵ Whaley, C.M., Briscoe, B., Kerber, R., O’Neill, B., Kofner, A. (2020). Nationwide Evaluation of Health Care Prices Paid by Private Health Plans. RAND Corporation. Available at: https://www.rand.org/pubs/research_reports/RR4394.html

³⁶ ICER. (2020). “2020-2023 Value Assessment Framework.” Available at: https://icer.org/wp-content/uploads/2020/10/ICER_2020_2023_VAF_102220.pdf

spending. Despite ICER’s 2019 announcement³⁷ on considering non-drug topics, to date, only two of ICER’s 44 assessments completed since that announcement have evaluated non-drug interventions. As stated by the Broader Value Initiative, in order to account for all aspects of value “we need to be able to see the entire street, not just the bit of sidewalk under the lamppost.”³⁸

VIII. ICER should embrace a transparent, credible, multi-stakeholder engagement approach to patient and stakeholder engagement.

PhRMA supports ICER’s planned steps toward an enhanced “Patient Engagement Program” (PEP), but they are insufficient for ensuring that patient feedback is meaningfully and quantitatively incorporated into ICER’s value assessment results. Meaningful patient engagement should adhere to and reflect work conducted by organizations such as the Innovation and Value Initiative,³⁹ the Patient Centered Outcomes Research Institute,⁴⁰ and the 10-step framework proposed by Mullins et al.⁴¹ This engagement should be done authentically and thus ICER should ensure that patient and advocate involvement goes beyond simple 'box-checking' to identify and incorporate patient-centered outcomes. Further, an independent patient council should regularly and transparently evaluate the impact of ICER’s PEP on value assessment results.

While PhRMA and ICER have disagreed about many issues in the past, we have appreciated past steps toward a transparent multi-stakeholder dialogue, such as holding open input periods, seeking feedback on proposed changes, and publishing stakeholder comments. This revised schedule of stakeholders opportunities to engage with ICER suggests many steps backward and the limitations of engagement with ICER in the future. ICER eliminated the open input period and significantly compressed both the timeline and length of comments.

	2020 VAF Update	2023 VAF Update
Open input period	39 days	none
ICER incorporation of open input	72 days	none
Public comment period on proposed changes	58 days; 10-page max	25 days; 5-page max
ICER incorporation of public comments	105 days	87 days
Total duration	274 days	112 days

³⁷ ICER. (2019). ICER Seeks Public Input to Guide Selection of Non-Drug Assessment Topics for 2020. Available at: https://icer.org/news-insights/press-releases/potential_2020_non-drug_topics/

³⁸ Broader Value Initiative. (2022). Background. Research Consortium for Health Care Value Assessment. Available at: <https://www.hcvalueassessment.org/broader-value-initiative-towards-more-value-assessment-health-services-and-procedures/background>

³⁹ The Innovation and Value Initiative. (2020). Partnering with Patients: Principles and Commitments. Available at: https://www.thevalueinitiative.org/wp-content/uploads/2020/05/2020-IVI-Partnering-with-Patients-Brief_Final.pdf

⁴⁰ Patient-Centered Outcomes Research Institute’s Advisory Panel on Patient Engagement. (2021). Equity and Inclusion Guiding Engagement Principles. PCORI. Available at: <https://www.pcori.org/about/pcoris-advisory-panels/advisory-panel-patient-engagement/equity-and-inclusion-guiding-engagement-principles>

⁴¹ Sofolahan-Oladeinde Y, Newhouse RP, Lavalley DC, Huang JC, Mullins CD. (2017). Early Assessment of the 10-Step Patient Engagement Framework for Patient-Centred Outcomes Research Studies: The First Three Steps. *Fam Pract*, 34(3):272-277. Available at: <https://academic.oup.com/fampra/article/34/3/272/3045930>

Of even greater concern is the deprioritization of stakeholder feedback for process and (selected) methodologic changes.⁴²

- “ICER may identify additional analyses within an assessment that are of relevance to policymaking such as shared-savings analyses. In such situations, ICER will highlight these analyses in the Draft Report and provide justification for their planned inclusion within ICER’s HBPB range in Final Reports.”
- “Going forward, these processes will be updated on an ad hoc basis, and will not follow the standard three-year update cycle that the ICER value assessment framework currently follows.”

We urge ICER to reconsider this truncated approach and to authentically seek public comment in these instances, and to do so with ample time and comment length to allow for meaningful stakeholder input and thoughtful, transparent consideration by ICER. Making quick ad hoc adjustments that may have far-reaching unintended consequences for patients does patients a grave disservice.

* * *

⁴² ICER. (2023). 2023 Value Assessment Framework Proposed Changes. p.13. Available at: https://icer.org/wp-content/uploads/2023/06/Proposed-VAF-Changes-For-Public-Comment-For-Publication_06052023.pdf

June 30, 2023

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, older adults 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 the Institute for Clinical and Economic Review's (ICER) proposed changes for its 2024 Value Assessment Framework.

Primarily, we reiterate our past comments and urge ICER to put patients and people with disabilities at the center of its assessments. While we share your interest in lowering health care spending and addressing affordability, ICER's use of value assessments methods that discriminate and fail to accurately capture outcomes that matter to patients only emboldens payers to use utilization management tools restricting patient access, thereby limiting the ability of patients and their providers to make decisions about the best treatment path for them. This puts the most vulnerable at an increased risk of worse health outcomes and 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 coverage of treatments that benefit their own bottom line. Yet, when patients and people with disabilities 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 health care system money.

We would urge ICER to use a lens centered on patients and people with disabilities as it updates its value framework. In in that spirit, we provide the following comments:

ICER continues to rely on metrics that devalue patients and what they care about.

In its proposed changes, ICER maintains its reliance on the discriminatory Quality-Adjusted Life Year (QALY) and the similarly flawed equal value of life-years gained (evLYG). We would like to strongly reiterate our criticism of the QALY and reinforce that the evLYG is not sufficient to address its methodological shortcomings.

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. The National Council on Disability (NCD), an independent federal agency, concluded in a

2019 report that QALYs place a lower value on treatments which extend the lives of people with chronic illnesses and disabilities, and that the use of the QALY violates the Americans with Disabilities Act (ADA). NCD therefore recommended that policymakers and insurers reject QALYs, indicating that the use of the QALY would be contrary to United States disability policy and civil rights laws.¹

Due to its discriminatory implications, QALYs and similar summary metrics of cost-effectiveness have been precluded from use in our public insurance programs. Medicare is prohibited by law from using a QALY-based threshold to determine coverage,² and in 1992, the George H.W. Bush administration determined state use of a QALY based system to determine Medicaid coverage would potentially violate the ADA.³

In its framework, ICER is seeking to provide payers and policymakers with an alternative to the QALY in the form of the evLYG, saying, “*we will emphasize that policymakers who prefer or who may be mandated to consider only measures of health gain other than the quality-adjusted life year (QALY) can find results at every threshold based solely on the equal value of life-years gained (evLYG).*” Yet, ICER recognized that the QALY is a problematic measure of health gain without addressing many of its failings. The evLYG is not a better substitute for the QALY and in fact has many of the same underlying shortcomings of the QALY, as it is built on the same faulty inputs.

The evLYG still fails to account for the full nuance in patient conditions when translating condition-specific measures into utility weights. Oftentimes, dimensions of data are lost when translating condition specific patient-reported outcome measures (PROs) into utility weights, and more frequently, ICER relies on generic PROs, like the EuroQoL instrument (EQ-5D). It is important that the dimensions used by instruments such as the EQ-5D bear some relationship to the QOL of patients, as emphasized by the U.S. Food and Drug Administration (FDA) in their guidance to industry on the use of the patient reported outcome (PRO).⁴ As such, the FDA notes that “*PRO instrument item generation is incomplete without a range of patients with the condition of interest to represent appropriate variations in severity and in population characteristics such as age or sex.*” The EQ-5D, translated into QALY utility weights, does not meet this standard as it relies upon weightings constructed by populations unfamiliar with the conditions being evaluated and therefore does not have the legitimacy obtained by consulting with patients. Criticism of this disconnect is widespread and growing.^{5,6} The EQ-5D often

¹ National Council on Disability, *Quality-adjusted Life Years and the Devaluation of Life with Disability*, 2019. https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf

² 111th Congress of the United States of America. (2010). H.R. 3590 The Patient Protection and Affordable Care Act. *Section 1182*. Washington, DC.

³ “Oregon Health Plan Is Unfair to the Disabled.” The New York Times, September 1, 1992. <https://www.nytimes.com/1992/09/01/opinion/1-oregon-health-plan-is-unfair-to-the-disabled-659492.html>.

⁴ US Food and Drug Administration *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. 2009. [2020-07-15].

⁵ Cubi-Molla P, Shah K, Burström K. Experience-Based Values: A Framework for Classifying Different Types of Experience in Health Valuation Research. *Patient*. 2018 Jun;11(3):253–270.

⁶ Helgesson G, Ernstsson O, Åström M, Burström K. Whom should we ask? A systematic literature review of the arguments regarding the most accurate source of information for valuation of health states. *Qual Life Res*. 2020 Jul;29(6):1465–1482

underestimates both the baseline burden of these diseases in patient populations, as well as the impact of treatments, compared to the more accurate disease-specific measures that were developed with those diseases in mind.⁷ Studies have shown that the content of the EQ-5D is often poorly aligned with patient perceptions in diseases such as asthma⁸, mental health⁹ and cancer,¹⁰ and whole population groups such as older adults.¹¹

ICER's attempt to shift focus to the evLYG in the wake of criticism of the QALY is concerning, as the evLYG does not solve many of the baseline issues that exist with the QALY. We encourage ICER to join the academic work ongoing by many other institutions to develop new alternative metrics that explicitly aim to exclude biases inherent to the QALY and better represent the needs, preferences, and outcomes of patients and people with disabilities.

ICER voices a desire to advance health equity but does not take simple actions to do so within its new framework.

We acknowledge the need for improvements in clinical trial diversity but were disappointed to see ICER's commentary imply that it can do nothing to address the limitation of diversity in trials in ICER's own modeling. There are reputable methodologies in economic modeling that have emerged in recent years to incorporate or address the problems of health inequalities – specifically, intervention-induced inequalities.^{12,13,14} ICER implies that these are not fit for this purpose and instead suggests that they should not be seen as a way of avoiding solving health inequality through policy. While we agree that changes must be made to ensure the clinical trial enterprise is prioritizing diversity, if ICER is continuing to conduct assessments without such diversity, ICER bears a responsibility to take every measure within its power to ensure its assessments are representative.

ICER has, in the past, acknowledged systematic health inequalities in the American healthcare system and committed to being part of the solution. ICER – and the payer community involved in its work – believes itself to be an arbiter of value, which directly affects current and future investment decisions in health care. This in turn impacts how – and to whom – healthcare is delivered and, ultimately, who benefits and who loses — the latter a detrimental loss to patients and communities already at a disadvantage. As a result, ICER does bear a moral responsibility to

⁷ Payakachat N, Ali MM, Tilford JM. Can the EQ-5D detect meaningful change? A systematic review. *Pharmacoeconomics*;2015;33:1137–1154.

⁸ Whalley D, Globe G, Crawford R, et al. Is the EQ-5D fit for purpose in asthma? Acceptability and content validity from the patient perspective. *Health Qual Life Outcomes*;2018;16:160.

⁹ Keetharuth AD, Rowen D, Bjorner JB, Brazier J. Estimating a preference-based index for mental health from the Recovering Quality of Life Measure: valuation of Recovering Quality of Life Utility Index. *Value Health*. 2021;24(2):281-290.

¹⁰ Garau M, Shah K, Towse A, Wang Q, Drummond M, Mason A. Assessment and appraisal of oncology medicines: does NICE's approach include all relevant elements? What can be learnt from international HTA experiences? Report for the Pharmaceutical Oncology Initiative (POI) February 2009.

¹¹ van Leeuwen KM, Jansen APD, Muntinga ME, Bosmans JE, Westerman MJ, van Tulder MW, et al. Exploration of the content validity and feasibility of the EQ-5D-3L, ICECAP-O and ASCOT in older adults. *BMC Health Serv Res*. 2015;15:1–10.

¹² Cookson R, Mirelman AJ, Griffin S, et al. Using Cost-Effectiveness Analysis to Address Health Equity Concerns. *Value Health*. 2017;20(2):206-212.

¹³ Round J, Paulden M. Incorporating equity in economic evaluations: a multi-attribute equity state approach. *Eur J Health Econ*. 2018;19(4):489-498

¹⁴ Avanceña ALV, Prosser LA. Examining Equity Effects of Health Interventions in Cost-Effectiveness Analysis: A Systematic Review. *Value Health*. 2021;24(1):136-143

evaluate the downstream effects of its decisions. Ignoring this reality will continue to perpetuate the health inequities that ICER claims a desire to help remedy.

ICER should acknowledge that no patient is average.

ICER states that its framework “takes a ‘population’ level perspective as opposed to trying to serve as a shared decision-making tool to be used by individual patients and their clinicians.” This statement does not acknowledge the reality that ICER has intentionally sought to establish itself in the payer community as an arbiter of value, and as such, ICER reports are being used frequently by PBMs and payers to make formulary decisions.¹⁵

The reality is that ICERs reports give one-size-fits-all results that oversimplify the value of new drugs by assuming an archetypal patient. Payer and PBM reliance on these reports then has the implication of limiting the physician’s ability to have robust shared decision-making conversations and prescribe a drug based on an individual patient. This can lead to significant harm to patients and people with disabilities for whom the drug in question would be highly effective and, in all likelihood, a highly cost-effective use of scarce health care resources in that context.

Ultimately, individuals will be the ones receiving the treatments which ICER reviews, and all of them are different. The “average” patient defined in ICER’s report is not a reasonable proxy for a real patient. The “average” patient is quite rare, and no more common than patients and people with disabilities at the wider edges of any random distribution.¹⁶ The reality is this patient archetype is not representative of most patients in a real-world setting, which challenges ICER’s value models.

While we appreciate that ICER seeks to address at least some aspects around the issue of heterogeneity of treatment effect, patient characteristics, and disease burden, it appears to be largely limited to approaching the validity of subgroup effects using a frequentist approach and traditional methods of measuring variance and uncertainty. We would encourage ICER to evolve beyond this thinking and look to newer innovations in subgroup analysis. The science of analyzing subgroup effects has developed considerably in the last few decades amid a growing acceptance of Bayesian techniques as a more effective approach to asking more complex multi-faceted questions such as identification of variance by subgroup. Stratification of patient characteristics is now almost solely conducted using Bayesian hierarchical models¹⁷ both in

¹⁵ Chambers JD, Enright DE, Panzer AD, Cohen JT, Ollendorf DA, Neumann PJ. Examining US commercial health plans’ use of The Institute for Clinical and Economic Review’s reports in specialty drug coverage decisions. *Journal of Managed Care & Specialty Pharmacy*. 2023 Mar;29(3):257-64.

¹⁶ Feinstein AR, Horwitz RI. Problems in the “evidence” of “evidence-based medicine”. *The American journal of medicine*. 1997 Dec 1;103(6):529-35.

¹⁷ Pennello G, Rothmann M. Bayesian subgroup analysis with hierarchical models. In *Biopharmaceutical Applied Statistics Symposium: Volume 2 Biostatistical Analysis of Clinical Trials* 2018 Aug 22 (pp. 175-192).

clinical evaluation¹⁸ or relative effectiveness^{19,20,21} and more recently in cost-effectiveness models.^{22,23}

On top of the advancement of methodological approaches to evaluating subgroup effects in evidence, multiple papers have highlighted the huge potential for subgroup analyses in economic modeling to improve overall health gain, in particular with respect to its ability to inform investment by targeting potential effects on reducing health disparities.^{24,25,26} If ICER is serious about its work helping move towards a more equitable health care system, it should be considering the concept of subgroup analyses from that perspective as well, not solely from the point of view of statistical methodology.

ICER puts significant focus on choosing model structures, calculating a utility value for a health state, or underlying mortality by age and sex. We would encourage ICER to transfer some of that effort into working in good faith to understand the variation of a drug's effectiveness in different patients.

ICER should pursue incorporation of caregiver benefits and costs in future modeling but also go further and rely on the societal perspective for its base case models.

We appreciate ICER's acknowledgement that it will incorporate caregiver benefits and costs along with productivity losses for patients and caregivers in future societal-perspective modeling. Patient groups have encouraged ICER to take this step for years and it is something that has been considered an essential component of cost-effectiveness methodology in the United States by the Second Panel on Cost-Effectiveness since the last panel in 2016.²⁷

Though we appreciate this incremental improvement, we are discouraged to see that ICER plans to continue to use the health care system perspective as its foundational perspective. The "health care system perspective" is not an accurate way to capture full value. It comes up short by failing to incorporate the values that accrue to the health care system via appropriate treatment, instead

¹⁸ Li N, Zhu W. A Bayesian approach for subgroup analysis. *Biometrical journal*. Biometrische Zeitschrift. 2023 Mar 12:e2200231-.

¹⁹ Pan J, Bunn V, Hupf B, Lin J. Bayesian Additive Regression Trees (BART) with covariate adjusted borrowing in subgroup analyses. *Journal of Biopharmaceutical Statistics*. 2022 Jul 4;32(4):613-26.

²⁰ Bunn V, Liu R, Lin J, Lin J. Flexible Bayesian subgroup analysis in early and confirmatory trials. *Contemporary Clinical Trials*. 2020 Nov 1;98:106149.

²¹ Jones HE, Ohlssen DI, Neuenschwander B, Racine A, Branson M. Bayesian models for subgroup analysis in clinical trials. *Clinical Trials*. 2011 Apr;8(2):129-43.

²² Nixon RM, Thompson SG. Methods for incorporating covariate adjustment, subgroup analysis and between-centre differences into cost-effectiveness evaluations. *Health economics*. 2005 Dec;14(12):1217-29.

²³ Burke JF, Sussman JB, Kent DM, Hayward RA. Three simple rules to ensure reasonably credible subgroup analyses. *Bmj*. 2015 Nov 4;351.

²⁴ Grutters, J.P., Sculpher, M., Briggs, A.H., Severens, J.L., Candel, M.J., Stahl, J.E., De Ruyscher, D., Boer, A., Ramaekers, B.L. and Joore, M.A., 2013. Acknowledging patient heterogeneity in economic evaluation: a systematic literature review. *Pharmacoeconomics*, 31, pp.111-123.

²⁵ Stevens, W. and Normand, C., 2004. Optimisation versus certainty: understanding the issue of heterogeneity in economic evaluation. *Social science & medicine*, 58(2), pp.315-320.

²⁶ Basu A, Grieve R, Pritchard D, Stevens W. One size does not always fit all in value assessment. *Am J Manag Care*. 2019 Nov 1;25(11):540-2.

²⁷ 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.

only focusing on payer benefit.²⁸ We continue to encourage ICER to move to a societal perspective for its base case models.

We would also encourage ICER to incorporate the caregiver health benefits accrued from reducing the burden on informal caregiving that result from more effective treatments. The United Kingdom's National Institute for Health and Care Excellence (NICE), which ICER leans heavily on for its approach to value assessment, has already included caregiver utility in its base-case cost-effectiveness models for diseases where informal caregiver burden is known to be high, such as Alzheimer's, Multiple Sclerosis and Parkinson's disease.²⁹ It is also the recommended perspective for cost-effectiveness models of the United States Second Panel on Cost-Effectiveness³⁰ and the International Society for Pharmacoeconomics and Outcomes Research.³¹

ICER continues to fall short in capturing dimensions of value that matter to patients and people with disabilities.

We were disheartened to see that, despite consistent recommendations from stakeholders including patient groups and recent exploration of the topic by respected entities like ISPOR, ICER has opted to omit “additional dimensions of value.”

ICER argues that including these additional dimensions risks double-counting. This feels like a manufactured excuse to not include dimensions of value that patient and caregiver stakeholders have shared are important to them. Many of the dimensions highlighted by ISPOR³² would certainly be immune from any double-counting concern as they are excluded from the standard measure of health benefits in standard cost or comparative effectiveness modeling.

One example is that of system effects. This is an area of investigation that tries to better reflect the true nature of complex health systems, and how improving efficiency in one area can lead to efficiency gains and resulting accrued health benefits in another area of health care since systems share key resources in practice. For example, if a new treatment for depression was both effective but also indirectly reduced the need for as much psychiatry time per patient, a known scarce resource,³³ greater access to psychiatry time would be available for a separate set of patients. This second set of patients' net health gain would rise indirectly. These types of benefits are deeply important to patients and standard modeling cannot capture them because they model all patients in a hypothetical vacuum where indirect effects are ignored by design. Capturing this

²⁸ Jena AB, Stevens W, Gonzalez YS, Marx SE, Juday T, Lakdawalla DN, Philipson TJ. The wider public health value of HCV treatment accrued by liver transplant recipients. *The American journal of managed care*. 2016 May;22(6 Spec No.):SP212-9.

²⁹ Afentou N, Jarl J, Gerdtham UG, Saha S. Economic evaluation of interventions in Parkinson's disease: a systematic literature review. *Movement disorders clinical practice*. 2019 Apr;6(4):282-90.

³⁰ 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.

³¹ Garrison Jr LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ispor drug cost task force report—Part II. *Value in Health*. 2010 Jan;13(1):8-13.

³² Lakdawalla DN, Doshi JA, Garrison Jr LP, Phelps CE, Basu A, Danzon PM. Defining elements of value in health care—a health economics approach: an ISPOR Special Task Force report [3]. *Value in Health*. 2018 Feb 1;21(2):131-9.

³³ Satiani A, Niedermier J, Satiani B, Svendsen DP. Projected workforce of psychiatrists in the United States: a population analysis. *Psychiatric Services*. 2018 Jun 1;69(6):710-3.

deeper dimension of impact on the health care system would benefit patients as well as health care decision makers.

As a real-world example of this, a recent study looked at the impact of systematic treatment of hepatitis C on waiting lists for liver transplants, not just for hepatitis patients but also other patients with chronic liver disease.¹⁸ Successful treatment of hepatitis C led to tens of thousands of non-hepatitis patients getting access to liver transplants and living longer lives as a result. It is clear the significant net health benefit this provides both for patients and society writ large. Standard cost-effectiveness modeling cannot capture this benefit. ICER has an opportunity to expand beyond standard modeling and capture broader and more accurate dimensions of value. It is unfortunate that ICER has chosen not to do this, and we would encourage it to reconsider this decision as it is developing its final framework revisions.

Additionally, ICER is now indicating that it accepts the importance of adjusting utility weights for the severity of the condition being treated, in response to a push from stakeholders that all conditions should not be treated equally and severity does matter.³⁴ Despite ICER acknowledging this reality, it is not proposing any real changes to its models. ICER solely plans to measure this level of severity for each disease it addresses using an evLYG shortfall but is not taking the further step of adjusting for relative severity in its modeling. Without incorporation in the actual models, the shortfall measures are simply paying lip service to the issue of severity weighting without actually incorporating it into ICER's methodology. This is also not in line with many health technology assessment systems in Europe that have begun to incorporate severity into modeling to make a more context-relevant case for any new technology,^{35,36} including NICE.³⁷ We encourage ICER to take the additional step of incorporating severity in its modeling, versus merely acknowledging it as an issue.

Conclusion

Thank you for your consideration of our suggestions on ways in which ICER can make its value assessments more fair and more equitable to patients. Please feel free to reach out to Sara van Geertruyden (sara@pipcpatients.org) in response to our recommendations above.

Sincerely,

ACMCRN Arachnoiditis & Chronic Meningitis Collaborative Research
Allergy & Asthma Network

³⁴ Sund B, Svensson M. Estimating a constant WTP for a QALY—a mission impossible? *The European Journal of Health Economics*. 2018 Jul;19(6):871-80.

³⁵ Barra, M. and K. Rand-Hendriksen, *A missing cornerstone in the Norwegian Priority Commission's weighting scheme—Sub-treatment balancedness is a necessary property for priority setting criteria*. *Nordic Journal of Health Economics*, 2016. 4(2): p. pp. 8-23.

³⁶ Swedish Parliamentary Priorities Commission, *Priorities in health care: ethics, economy, implementation*. 1995, Stockholm: Swedish Government.

³⁷ Collins C, Cheng J, Taylor I, Mumford A. HTA73 Evaluation of NICE Severity Modifiers. *Value in Health*. 2022 Dec 1;25(12):S310.

Allfocus Technologies, Inc.
Alliance for Aging Research
Alliance for Patient Access
Allies for Independence
ALS Association
American Association of Kidney Patients
American Association on Health and Disability
American Behcet's Disease Association (ABDA)
Asthma and Allergy Foundation of America
Axis Advocacy
Bladder Cancer Advocacy Network
Buscher Consulting
Cancer Support Community
CancerCare
Caring Ambassadors Program
Celiac Disease Foundation
Center for Autism and Related Disorders
Coalition of Texans with Disabilities
Color of Crohn's and Chronic Illness
Congenital Hyperinsulinism International
Crohn's & Colitis Foundation
Cutaneous Lymphoma Foundation
Cystic Fibrosis Research Institute
Davis Phinney Foundation for Parkinson's
Derma Care Access Network
Diabetes Leadership Council
Diabetes Patient Advocacy Coalition
Disability Rights Oregon
Emily's Entourage
Epilepsy Alliance America
Epilepsy Foundation
Epilepsy Foundation New England
Familia Unida Living with MS
Family Voices of California
Genetic Alliance
Global Liver Institute
GO2 for Lung Cancer
Health Hats
HealthHIV
Hermansky-Pudlak Syndrome Network
Huntington's Disease Society of America
Hypertrophic Cardiomyopathy Association
ICAN, International Cancer Advocacy Network
International Pemphigus Pemphigoid Foundation
Lakeshore Foundation
Mary Vought, Former NCD Member

Miles for Cystic Fibrosis
MLD Foundation
Multiple Sclerosis Foundation
National Alliance for Hispanic Health
National Center for Parent Leadership, Advocacy, and Community Empowerment (National PLACE)
National Disability Rights Network (NDRN)
National Organization of Nurses with Disabilities
Not Dead Yet
Partnership to Fight Chronic Disease (PFCD)
Partnership to Improve Patient Care
Patients' Rights Action Fund
Preparedness and Treatment Equity Coalition
PXE International
Rare New England
RASopathies Network
Rosie Bartel
Second Thoughts MA: Disability Rights Advocates against Assisted Suicide
SYNGAP1 Foundation
The Bonnell Foundation: living with cystic fibrosis
The Coelho Center for Disability Law, Policy and Innovation
The Headache & Migraine Policy Forum
The Hepatitis C Mentor and Support Group-HCMSG
TSC Alliance
United Spinal Association
Usher 1F Collaborative
Usher Syndrome Coalition
Whistleblowers of America

June 30th, 2023

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review (ICER)
14 Beacon Street, Suite 800
Boston, MA 02108

Dear Dr. Pearson,

Sandoz appreciates the opportunity to provide feedback on the Institute for Clinical and Economic Review's (ICER) draft proposed changes to the value assessment framework titled "2023 Value Assessment Framework – Proposed Changes" and draft proposed changes to ICER's conduction of value assessments titled "ICER Processes for Conducting Value Assessments – Proposed Changes." In summary, Sandoz respectfully offers the following suggestions for consideration:

- Align Clinical Diversity Ratings with guidance from FDA;
- Use established tools when considering RWE studies; and
- Consider healthcare sustainability as an important attribute in Benefits Beyond Health and Special Ethical Priorities.

Sandoz supports increased patient voice and engagement and looks forward to how patient considerations are implemented in future assessments.

Align Clinical Trial Diversity Efforts with the FDA

Section 2.1 "Clinical Trial Diversity" states that "ICER will provide an overall diversity rating for the following demographic characteristics: race/ethnicity, sex, and age, specifically, adults aged 65 and older." While Sandoz supports efforts to improve clinical trial diversity, we caution that the application of such diversity ratings should be aligned with guidance from the FDA for improving diversity within clinical trials (currently in draft form).¹ As acknowledged by the FDA, the purpose of increasing clinical trial diversity is to "potentially identify effects on safety

or efficacy outcomes that may be associated with, or occur more frequently within these populations.”¹

While increasing clinical trial diversity is clearly a laudable goal, it is challenging to apply this to clinical studies that are conducted to support biosimilar development. The scientific and regulatory question answered by clinical trials for biosimilar products (biosimilars) is **not** to replicate safety or efficacy outcomes already evaluated by the reference product’s manufacturer. Rather, the goal of biosimilar development is to demonstrate that there are no clinically meaningful differences to an FDA-approved reference product through a totality-of-the-evidence approach that includes “a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness.”² Accordingly, the ideal clinical comparative study for a biosimilar would be conducted within a homogenous patient population demonstrated to have experienced a robust treatment effect, using an adequately sensitive endpoint.²⁻⁴ Indeed, the FDA draft guidance on improving enrollment for underrepresented populations only recommends diversity plans for 351(a), 505(b)(1), and 505(b)(2) applications, and excludes 351(k) applications for biosimilars.¹

Currently, it is unclear how ICER plans to apply Clinical Trial Diversity ratings to biosimilars. As an FDA-approved product, a biosimilar would have met the standard of “no clinically meaningful difference” to its reference product; accordingly, the safety and efficacy effects of a reference product on various subpopulations will also pertain to their corresponding biosimilars. Since the availability of biosimilars have the potential to expand access to appropriate treatment options, biosimilar studies that include diverse populations of patients will be more relevant in real-world settings.⁵ All of these considerations are equally relevant for Section 2.2 “Subpopulation Analyses.”

Use Established Tools When Considering RWE Studies

Sandoz supports the inclusion of real-world evidence (RWE) studies in future assessments, as mentioned in section 3.5 “Other Changes” for both comparative clinical effectiveness and economic model evaluations. In addition to updating previous ICER findings with real world data (RWD) from RWE studies, Sandoz encourages ICER to evaluate the quality and methodology of included RWE studies, using previously established tools such as The Professional Society for Health Economics and Outcomes Research (ISPOR) checklist for prospective observational studies, the ISPOR checklist for retrospective database studies, and the combined Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort, case-control, and cross-sectional study designs.⁶⁻⁸ Furthermore, RWE can be useful in evaluating and supporting diversity goals with both reference products and biosimilars.

Consider Sustainability Within the Healthcare System as Additional Benefits Beyond Health and Special Ethical Priorities

Section 1.2. “The Population Perspective and Intended Uses of the ICER Value Framework” discusses that the ICER value framework is meant to take a “population-level” perspective that supports population-level decisions and policies. In addition, the proposed changes include renamed sections “Benefits Beyond Health” and “Special Ethical Priorities” from the previous “Potential Other Benefits or Disadvantages” and “Contextual Considerations” that aim to capture

“other aspects of value from both the patient perspective and that of the health system and society that are either unmeasured in clinical trials or that reflect social or ethical values that in some way may influence the relative weight decision-makers place on health gains and uncertainty when making an overall judgment of value for money for any specific new treatment option.”

Sandoz would like to introduce the concept of sustainability as another important contextual consideration when evaluating healthcare from both a population health and ethical priority, especially considering today’s landscape of continuously rising healthcare costs and increasingly complex allocation decisions that ICER aims to clarify. One of the main value pillars of biosimilars is the economic impact of providing less costly medications relative to reference products with the goals of maintaining patient treatment access, choice within biological medications, and financial relief within the overall healthcare system that can be applied to continued innovation of new medications.⁹ This further leads to continued competition within the market, reliable channels of biological product supply chains, and sustainability to the healthcare system.⁹ Highlighting efforts within the industry to combat rising costs and increase sustainability should be considered in ICER’s updated value assessment framework. Further, ICER should be cautious in “generat[ing] cost-effectiveness findings assuming that new drugs and some comparator drugs will be subject to CMS price negotiation at a future time point,” given that some of these products may also likely have impending biosimilar competition. ICER reviews should not result in the unintended consequence of discouraging competition; the sustainability of the biosimilar market is integral to the sustainability of the overall healthcare system.

Sandoz Supports Increased Patient Stakeholder Engagement

Sandoz encourages ICER to include the patient voice as mentioned in Section A3.2.1. “Patient Engagement Program.” Many of the initiatives include addressing barriers to patient participation with ICER and coordinating discussions with patients and caregivers. ICER should consider additional ways to engage and provide outreach to disease specific patient advocacy groups to effectively collaborate. Sandoz looks forward to how feedback and suggestions from patients and caregivers will be implemented in future value assessments to improve patient representation and outcomes.

Sincerely,

Anna Chen, PharmD, MS
Associate Director, HEOR

Edward Li, PharmD, MPH
Head, HEOR and Oncology

US Medical Affairs
Sandoz Biosimilars

References:

- 1) U.S. Food and Drug Administration. Diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials; draft guidance for industry 2022. <https://www.fda.gov/media/157635/download>. Accessed June 26th, 2023,
- 2) US Food & Drug Administration website. Scientific considerations in demonstrating biosimilarity to a reference product. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product>. Accessed June 22, 2023.
- 3) Thill M. Biosimilar Trastuzumab in Clinical Trials: Differences or Not?. *Breast Care (Basel)*. 2019;14(1):17-22. doi:10.1159/000496503
- 4) Stebbing J, Mainwaring PN, Curigliano G, et al. Understanding the Role of Comparative Clinical Studies in the Development of Oncology Biosimilars. *J Clin Oncol*. 2020;38(10):1070-1080. doi:10.1200/JCO.19.02953
- 5) Boccia R, Jacobs I, Popovian R, de Lima Lopes G Jr. Can biosimilars help achieve the goals of US health care reform?. *Cancer Manag Res*. 2017;9:197-205. Published 2017 Jun 1. doi:10.2147/CMAR.S133442
- 6) Berger ML, Dreyer N, Anderson F, Towse A, Sedrakyan A, Normand SL. Prospective observational studies to assess comparative effectiveness: the ISPOR Good Research Practices Task Force Report. *Value Health*. 2012;15(2):217-230.
- 7) Motheral B, Brooks J, Clark MA, et al. A checklist for retroactive database studies – report of the ISPOR Task Force on Retrospective Databases. *Value Health*. 2003;6(2):90-97.
- 8) von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008 Apr;61(4):344-9.
- 9) IQVIA Institute for Human Data Science. *Spotlight on Biosimilars: Optimizing the Sustainability of Healthcare Systems*. <https://www.iqvia.com/insights/the-iqvia-institute/reports/spotlight-on-biosimilars>. Published 2021. Accessed June 22nd, 2023.



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

•
Boston, June 29, 2023

RE: “ICER Proposes Updates to Value Assessment Framework Methods and Procedures”

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson,

Sanofi is pleased to provide comments to the Institute for Clinical and Economic Review’s (ICER) request for open input on the planned update of its value assessment framework (VAF) ¹.

We appreciate ICER’s ongoing willingness to engage on their VAF, as evidenced through previous consultations and evolution of their framework. It is in this spirit that we share our current views on how to ensure the VAF keeps pace with the purpose for which it is intended.

We reiterate our prior recommendation that ICER adopt a comprehensive conceptualization of value in its statement of the purpose and principles of the VAF ⁽²⁻⁴⁾.

Sanofi stands for a holistic, sustainable, and transparent definition of value that incorporates clinical, economic, and societal perspectives across the lifecycle of our medicines and vaccines with a key objective of improving patient outcomes while supporting innovation and healthcare system efficiency. In this spirit, we provide you with our comments on the following pages.



1. Clinical Trial Diversity

*To encourage and promote the racial and ethnic diversity of US disease population in multinational clinical trials. ICER's reports will include a new subsection called "Clinical Trial Diversity" where the overall diversity in race/ethnicity, sex, and age, specifically, adults aged 65 and above will be rated. This rating will focus only on the subgroup of patients recruited **exclusively in US**.*

While Sanofi welcomes the needed to enhance the diversity of clinical trial, it should not be done at the detriment of the quality of the study and should therefore consider the complexity of multistate and multisite trial design and differences in practice, especially when recruiting in some indications

- We feel there is some ambiguity in the objective which is either to assess the trial representativeness of the racial and ethnic diversity of the US population or of the racial and ethnic diversity of the US population that has the studied disease. We believe that this is the latter which should be addressed.
- We understood that this would apply to the clinical trials run/sponsored by the manufacturer and not to trials that have been gathered through literature search to build relative effectiveness, although some clarification might be helpful.
- We respectfully ask ICER to consider the difficulty in recruiting patients in some indications, e.g. in rare diseases, which leads to higher challenge to meet the racial and ethnic diversity criteria.
- This rating approach may penalize multinational clinical trial design where overall targeted population representativeness is ensured but the US population is somehow too small to fulfill the requirements stated by the new recommendation.

2. Subpopulation Analyses

ICER is planning to include an a priori list of the subpopulation whose relevance will rely on clinical experts, patients, patient groups, and other stakeholders' perspectives. Race, sex, and age will be considered as a presumptive subpopulation for every review

- Subgroups' patient characteristics are not systematically reported (even less when subgroups are not prespecified) and studies may not be powered enough to show differences in the selected subgroups. Not being able to show or not showing does not mean that there is no proof of difference. We were wondering how ICER will fairly compare subgroups between studies, especially for drugs for which such data are not available.
- As a result of this subpopulation list, would the manufacturers be asked to provide post-hoc analyses including those subgroups? Would manufacturers be involved in scoping discussions?

3. Perspective in Economic Models

The cost-effectiveness results will be reported from both the health care system perspective and a modified societal perspective.

- We appreciate that ICER considers including more societal impact of the disease burden, however, in the common case of slowly progressive rare diseases, patients tend to adjust to their condition so that the health-related quality of life as measured through generic preference-based measures is lacking sensitivity and gives higher values than expected as regards the severity of the disease. In that example the societal perspective might also underestimate the indirect effect.
- We would appreciate having more insights on how the 75% is calculated in the following sentence “Since no parallel relationship between patient utility scores and career time use data exists for the US setting, ICER will assume that career time spent is proportional to 75% of patient formal labor time. This estimate is based on the modeled relationship between career time required and patient time lost according to patient utility scores in the United Kingdom setting.”
- How is ICER considering the career utility gain/loss in this broader modified societal perspective, knowing that the career is impacted not only the productivity aspect but also on his/her quality of life?

4. Dynamic Pricing Scenario

Some new drugs, especially those targeted to Medicare-eligible populations may have a price decrease as described in the Inflation Reduction Act, at the ICER assessment time. A dynamic pricing scenario will be run for small molecule and biological products that are predominantly targeted to Medicare-eligible populations and likely to have price decrease over the model time horizon.

- Please clarify whether the dynamic pricing scenario should apply to the evaluated product in question or if it should also involve any drug involved in the economic evaluation.
- The loss of exclusivity and Medicare price negotiation will take place on a regular basis over time; currently, only price decrease is considered in this scenario. Will ICER consider only price decreases that occurred at the time of the assessment or all price decreases before and over the model time horizon? In the latter case, please clarify to what extent this exclusively decreasing pricing scenario will converge towards an economically unrealistic price. Especially since this scenario will only target chronic therapies for which the model time horizon is often lifetime.
- Moreover, knowing that a part of this price decrease process will be a negotiation, with the little hindsight on real life price decrease scenario, we encourage ICER to continue working to improve the implementation of this scenario.



- We reiterate Sanofi’s VAF principles: value should be comprehensively defined, encompassing clear and multidimensional value criteria reflecting full clinical, economic, and societal value of innovative medicines.
- The proposed dynamic pricing scenario for products predominantly targeted to Medicare-eligible populations conceptually makes sense but does not explicitly consider the Inflation Reduction Act (“IRA”) exclusion criteria for: orphan products with one indication, products with Medicare sales \$200 million or less, biosimilar or generic comes to market.

5. Other Changes

ICER is intending to update its reference case in including the above-mentioned changes and continue to seek opportunities to use real-world evidence within its assessments

- We appreciate that ICER considers the important role that real world evidence (RWE) plays to address research questions that are relevant to investment decisions and cannot be addressed by randomized controlled trials (RCTs). Consideration should be given to adopting a high-level consensus framework on the types of research questions that can be addressed by RWE to promote acceptance and consistency of RWE in health technology assessment.

6. Other Sanofi comments:

- In the VAF 2020-2023, there was no clarification about what EQ-5D version ICER would prefer (3L/5L). It also seems that the US algorithm developed on US population is preferred, but it still not clearly stated. Could we suggest a clarification as a next ICER VAF topic?

We thank ICER for soliciting input on the planned update of its value assessment framework, and hope that you consider our recommendations. We are happy to engage in additional dialogue on these issues or otherwise assist at any time.

Yours sincerely,

Kyle Hvidsten

*Head, Specialty Care HEVA
Global Market Access, Sanofi*



References:

1. ICER Proposes Updates to Value Assessment Framework Methods and Procedures. <https://icer.org/wp-content/uploads/2023/06/Proposed-VAF-Changes-For-Public-Comment-For-Publication-06052023.pdf>. June 5, 2023. Accessed June 5, 2023
2. Sanofi. Comments to ICER, “ICER Opens National Call for Proposed Improvements to its Value Assessment Framework” Submitted September 12, 2016.
3. Sanofi. Comments to ICER, “Overview of the ICER value framework and proposals for an update for 2017-1018”. Submitted April 3, 2017.
4. Sanofi. Comments to ICER, “Proposed value assessment framework for treatments that represent a potential major advance for serious ultra-rare conditions”. Submitted September 22, 2017



June 30, 2023

Submitted electronically to publiccomments@icer.org.

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

Re: Methods Update: Value Assessment Framework

Dear Dr. Pearson:

The Society for Women's Health Research (SWHR) appreciates the opportunity to provide input to the Institute for Clinical and Economic Review (ICER) on its Methods Update: Value Assessment Framework.

SWHR, a more than 30-year-old national nonprofit organization based in Washington, D.C., is widely recognized as a thought leader in promoting research on biological sex differences in disease and eliminating imbalances in care for women through our science, policy, and education work.

As an organization whose focus centers on raising awareness of the unique needs of women and closing knowledge and health care gaps, SWHR is committed to ensuring that health care value assessments account for women and their diverse needs as patients, caregivers, and often as the chief health decision maker of the family. We therefore submit the following comments for ICER's consideration as it works to finalize its 2024 Health Care Value Assessment Framework.

Recognizing the Uniqueness of Each Patient

Within the document of proposed changes, ICER states that to inform medical policies, it "takes a 'population' level perspective as opposed to trying to serve as a shared decision-making tool to be used by individual patients and their clinicians."

While SWHR acknowledges that ICER is attempting to "support deliberation on medical policies," ICER's reports are being utilized by payers and other stakeholders in order to make formulary decisions.¹ As a result, this population-level, one-size-fits-most approach oversimplifies the value of new drugs by ascribing certain characteristics to patients regardless of individual circumstances. As SWHR notes in its Policy Principles: Health Care Value Assessment, "Patient subpopulations can differ in their response to a given therapy (i.e.,

¹ Chambers JD, Enright DE, Panzer AD, Cohen JT, Ollendorf DA, Neumann PJ. Examining US commercial health plans' use of The Institute for Clinical and Economic Review's reports in specialty drug coverage decisions. *Journal of Managed Care & Specialty Pharmacy*. 2023 Mar;29(3):257-64.

heterogeneity of treatment effect). Therefore, value assessments for new therapies should take into consideration factors, such as patients who cannot tolerate currently available therapies, are contraindicated for these therapies, have heterogeneous responses to these therapies, or for whom these therapies are ineffective or whose conditions have progressed.” Further, values are dynamic and change over time as patients’ individual circumstances and experience of treatment and illness evolve throughout the course of disease. Making decisions based on an “average” patient, especially when it can affect coverage decisions that could have implications for care, could do a major disservice to those who are relying on a given treatment.

SWHR appreciates ICER’s acknowledgement that within value assessment frameworks there is an “inherent tension between average findings in clinical studies and the uniqueness of every patient” and that there is “diversity in the way that patients view the balance of risks and benefits of different treatment options.” SWHR also appreciates that ICER will continue to include a “Heterogeneity in Subgroups” to review subgroup effects of a given treatment. However, SWHR is concerned that a “population-level” focus could have negative unintended consequences when it comes to not only to a physician’s ability to prescribe a certain medication to a patient, but also to a patient’s ability to access the said medication due to cost.

Ensuring Clinical Trial Diversity

ICER states that it will provide an overall diversity rating for the demographic characteristics of “race/ethnicity, sex, and age, specifically among adults 65 and older.”

SWHR supports policies and practices that ensure trial participation reflects the overarching patient/treatment population as well as policies that allow data to be disaggregated by key demographic information. SWHR strongly encourages ICER to separate race and ethnicity. As noted in a 2021 *JAMA* editorial, race and ethnicity “have important, albeit contested, social meanings. Neglecting to report race and ethnicity in health and medical research disregards the reality of social stratification, injustices, and inequities and implications for population health, and removing race and ethnicity from research may conceal health disparities.”²

Additionally, SWHR would urge ICER to consider both sex and gender as part of its demographic consideration. Incorporating both sex and gender data analysis will allow for better data analysis, which could in turn, lead to improved health outcomes.

Weighing Use of Certain Metrics

SWHR echoes the concerns of the Partnership to Improve Patient Care (PIPC) regarding ICER’s reliance on Quality-Adjusted Life Years (QALY) as a measure of disease burden. This subjective measure may overlook certain health equity considerations and may limit the health benefits that can be captured. As noted in the 2019 National Council on Disability’s (NCD) report on

² Flanagin A, Frey T, Christiansen SL, AMA Manual of Style Committee. Updated Guidance on the Reporting of Race and Ethnicity in Medical and Science Journals. *JAMA*. 2021;326(7):621–627. doi:10.1001/jama.2021.13304

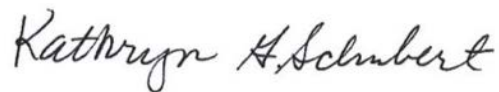
QALYs,³ the NCD found “sufficient evidence of the discriminatory effects of QALYs to warrant concern, including concerns raised by bioethicists, patient rights groups, and disability rights advocates about the limited access to lifesaving medications for chronic illnesses in countries where QALYs are frequently used.”

While SWHR acknowledges ICER’s comment that it will emphasize that “policymakers who prefer or who may be mandated to consider only measures of health gain other than QALYs find results at every threshold based solely on the equal value of life-years gained (evLYG),” the Society remains concerned about the continued presence of QALYs within the Framework and recognizes that groups, such as PIPC, believe that the evLYG measure “has many of the same underlying shortcomings of the QALY.”

SWHR encourages that ICER continue to explore measures that will better represent the unique needs and preferences of patients and people with disabilities.

Thank you for the opportunity to provide comment on ICER’s Methods Update: Health Care Value Assessment Framework. If you have questions about the information included above, please do not hesitate to contact me at kathryn@swhr.org.

Sincerely,

A handwritten signature in cursive script that reads "Kathryn G. Schubert".

Kathryn G. Schubert, MPP
President and Chief Executive Officer
Society for Women’s Health Research

³ Quality-Adjusted Life Years and the Devaluation of Life with Disability, National Council on Disabilities. November 2019. https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf. Accessed 30 June 2023.

June 30, 2023

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

Submitted electronically at: publiccomments@icer.org

Re: Request for Public Input for 2023 Value Assessment Framework Proposed Changes

To Whom It May Concern:

UCB is a global biopharmaceutical company with U.S. headquarters located in Atlanta, Georgia. With more than 8,700 employees globally, we are inspired by patients and driven by science. Our focus is on innovating new medicines to treat severe, chronic neurological, immunological, and rare conditions. 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. We recognize our responsibility, as part of the value chain, to patients, the healthcare system, and society at large and are dedicated to working toward a more sustainable healthcare system. As such, UCB appreciates the opportunity to provide comments on the Institute for Clinical and Economic Review (ICER) 2023 Value Assessment Framework (VAF) Proposed Changes. ICER's evidence reports have a significant impact on patient access to life-changing and life-saving medicines; for this reason, it is crucial that the value assessment framework's underlying methodologies are sound and validated, and their potential impact on patients is understood. UCB offers the following comments for ICER's consideration.

I. Process

While UCB appreciates the opportunity to provide comment on ICER's proposed 2023 VAF revisions, we are disappointed ICER limited the opportunity for stakeholder feedback in the process. Previous updates to the VAF have allowed two opportunities for stakeholder feedback: prior to issuing the proposed changes to the VAF and after the proposals are released. The 2023 revision process skipped the first opportunity for stakeholder engagement by releasing proposed revisions without taking initial stakeholder feedback. In addition, ICER is only allowing a 25-day (19 business day) comment period for stakeholders to process proposed revisions and finalize comments. Such a short time period does not offer meaningful opportunity for stakeholders to provide feedback on the proposed changes, particularly given ICER's document is brief and light on details. UCB is disappointed ICER's process for updating its VAF is condensed, opaque, and does not afford opportunity for meaningful stakeholder feedback.

II. Clinical Trial Diversity

At UCB, we are committed to working toward a clinical trial infrastructure that addresses health disparities and closes the gap in clinical trial diversity. Driving meaningful change on a broader level requires investment, transparency, accountability, and partnerships across key stakeholders. However, we question whether ICER is the most relevant, equipped organization for addressing clinical trial diversity issues, as described in the proposed VAF changes.

Rather than incorporating clinical trial diversity into its VAF, UCB encourages ICER to focus on revising its framework to address other meaningful issues with health equity present in its framework – e.g., its reliance on quality-adjusted life years (QALYs) – and holistically assessing the implications of HTA on health equity. HTAs should seek to advance equity by ensuring that patients have a meaningful voice in the HTA process, improve the evidence base to remove implicit biases, and appreciate that HTA can be a contributor to inequity and bias.ⁱ

Should ICER choose to move forward with finalizing this revision, UCB offers the following, specific comments on the proposal:

1. UCB requests clarification regarding the data source from which ICER plans to obtain demographic information about clinical trial participants.
2. ICER proposes to use its own framework in order to “objectively and consistently” rate demographics across all ICER assessments. Not only does ICER rely only on its own frameworkⁱⁱ, but in the framework, it highlights several important limitationsⁱⁱⁱ which include failing to perform a systematic review of methods or engaging stakeholders for comment. UCB is concerned this approach may be a bit myopic and urges ICER to engage with other HTA organizations and stakeholders to improve the framework.
3. When estimating disease-specific prevalence, ICER proposes to compare clinical trial participants to population estimates and interpret the finding accordingly. UCB has concerns about this approach, particularly in the case of rare and ultra-rare diseases. The general population is not an appropriate comparator to a population suffering from a specific condition. When attempting to determine the prevalence of a disease state, the analysis should be weighted relative to the overall prevalence of the disease state within a certain population. For example, hidradenitis suppurativa (HS) is more prevalent in African American populations, while the patient population in myasthenia gravis (MG) skews younger and female versus older and male. At a minimum, factors such as race and ethnicity should be considered when attempting to extrapolate disease prevalence. UCB further suggests ICER engage stakeholders such as patient advocacy groups, healthcare providers, and manufacturers for assistance in determining disease prevalence, particularly in the case of rare and ultra-rare diseases.
4. UCB appreciates ICER’s use of the participation to prevalence ratio, but requests clarity regarding how ICER will consider this ratio when prevalence data is not available; specifically, in the case of rare and ultra-rare diseases and disease states where subgroups have rarely, if ever, been included.
5. Additionally, UCB is concerned by ICER’s proposal to rate the demographic diversity of clinical trials. Publicly available data already shows the demographics of clinical trials;

rating the demographic diversity of a trial will not add additional value and has the potential to be predictive and biased. By way of example, for the drug Ozempic – although obesity and diabetes are leading indications in people of color, the snapshot of the trial diversity expresses that only 6% were Black and 12% were Asian, a misleading determination.^{iv}

6. UCB encourages ICER to broaden the demographic categories included in its rating system. Specifically, we urge ICER, where appropriate, to assess pediatric representation as pediatric patients are already an underrepresented demographic, and to include American Indian or Alaskan Native, Native Hawaiian, and other Pacific Islanders in its assessment, as these demographic groups have a higher rate of disease than any other in the U.S.

III. Subpopulation Analyses

ICER proposes to rely on a targeted literature review and interviews with patient and clinical experts to scope the most relevant subpopulations. UCB requests additional information regarding how ICER plans to engage with stakeholders to identify those subpopulations. Additionally, UCB suggests ICER include manufacturers in this process as they may often be in the best position to identify those subpopulations.

ICER's proposed presumptive subpopulations of race, sex, and age are too narrow; UCB encourages ICER to consider additional subpopulations, such as disability/ability, geographic location, and socioeconomic status. UCB has concerns about how ICER's proposed approach will account for heterogeneous diseases, such as MG. In a previous report,^v ICER acknowledged that MG is an extremely heterogeneous disease, varying not just patient-to-patient but hour-to-hour within a single patient. The nature of the disease further complicates the already complex world of rare disease and the subjective nature of the treatment approaches from physician-to-physician and patient-to-patient. ICER's proposed subpopulation approach does not seem to adequately account for this dynamic. UCB encourages ICER to consider revising its approach to reinforce the need for more targeted therapies and solutions to meet the unique needs of patients with rare disease.

IV. Long-Term Cost-Effectiveness

UCB is disappointed ICER has abandoned previously committed-to efforts to explore alternative value assessment methods. The QALY is largely recognized as outmoded and problematic.^{vi} The measurement ignores measures of value that matter to patients and caregivers. The metric is inherently subjective regarding quality-of-life estimates and thresholds, and raises concerns about its potential to limit patient access to treatments. Most concerning is the issue of QALY discriminating against the elderly, disabled, and terminally ill by assigning a lower value to their lives compared to others. Using QALY fails to capture a wide variety of other benefits that a successful therapy can have, including a person's return to economic productivity, their performance in school, ability to function as a caregiver for others, and so on. Not all treatments are intended to extend a person's life. For example, therapies for rheumatoid arthritis (RA) are, instead, intended to improve a person's quality of life. On the other hand, cancer treatments are almost exclusively intended to increase longevity. By applying the same one-size-fits-all

formula to evaluating differing treatments for different diseases, ICER's approach ignores what patients value most to address their unique circumstances and conditions.

The Equal Value of Life Years Gained (evLYG) metric is an improvement over the QALY; however, it has its own discriminatory implications. For example, the evLYG devalues treatments for diseases that do not extend life expectancy but rather impact quality of life – such as mental health, RA, back pain, etc. – although these treatments improve the lives of patients and caregivers.^{vii}

The use of the evLYG, alongside the QALY still does not do enough to eliminate the discriminatory aspects of the QALY. UCB encourages ICER to explore alternative metrics, such as cost-per-outcome or willingness to pay thresholds. 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.

UCB is concerned that, should ICER's VAF not evolve to capture more elements of value, its benchmarks will not reflect a truly value-based assessment or price of a treatment. We encourage ICER to consider alternative methods that would take a more nuanced approach to assessing value in developing treatments and consider the elements of value most important to patients. Additionally, in the absence of data, it would be helpful if ICER would explain how alternate scenarios would be explored and how the approach will be adjusted depending on the condition being assessed. Anytime there is a reference to cost-effectiveness, the assessment should clarify any and all assumptions the assessor relied on, as well as any uncertainties around the data used to assess that output. It is critical that decision-makers understand that: 1) the cost-effectiveness of a treatment can vary significantly across patient segments due to different patient needs; and 2) the cost-effectiveness of a treatment is based on significant assumptions about the data. Particularly, in the wake of the changes to the market under the Inflation Reduction Act (IRA), it is imperative to discourage assessments that could further limit patients' access to necessary treatments.

V. Dynamic Pricing Scenario

UCB is encouraged ICER is proposing to account for dynamic pricing rather than relying on static pricing. Given prices in the U.S. may vary over time, incorporating price trajectories and/or conducting or updating the assessment over the lifecycle of a product will better account for long-term costs. However, only including changes due to the IRA's negotiation program – i.e., Maximum Fair Price (MFP) – in its consideration of dynamic pricing leads to a significant likelihood of a distorted result. Only looking at the price change of medicines under the IRA negotiation program, without incorporating other potential changes – e.g., the impact of generics, competition in the marketplace – could lead to misleading or, at best, not meaningful results. We strongly encourage ICER to consider dynamic pricing more broadly, taking into account other factors of change rather than solely considering MFP pricing under the IRA.

VI. Quantifying Additional Dimensions of Value

UCB is encouraged that ICER proposes to include consideration of unmet need alongside the findings to support deliberations on the long-term value for money of treatments. However, we request that ICER include the definition of “unmet need” it will consider as part of its deliberations.

We encourage ICER to continue to investigate and improve on ways to incorporate additional dimensions of value. Other value assessment frameworks^{viii} have evolved to include additional dimensions of value more formally and, as a result, may be better positioned to provide a more holistic evaluation of cost-effectiveness and value. UCB urges ICER to recognize the value of these considerations in both the clinical differentiation assessment and the base-case cost-effectiveness model. Ideally, ICER would incorporate these additional dimensions of value into the base-case alongside the healthcare perspective. UCB also encourages ICER to be transparent by specifically identifying which elements are quantifiable, and which are not. Lastly, we recommend that ICER continue engaging with stakeholders to explore ways to quantify additional dimensions of value. UCB is disappointed ICER continues to ignore important elements of value that matter to patients, underestimating the value of many treatments despite substantial stakeholder feedback to the contrary.

VII. Health Benefit Price Benchmarks

UCB encourages ICER to maintain or, ideally, increase the effective threshold range for price benchmarks in order to avoid negative impacts on patients’ access to needed treatments. UCB has serious concerns about the harmful effects these thresholds may have for cell and gene therapies and treatments for rare and ultra-rare diseases. Particularly, as time goes on these thresholds are not sustainable. Prices of treatments, goods, and services typically increase over time; therefore, \$100,000 is not as valuable today as it was when first proposed, nor will it continue to be as valuable in the future as new, innovative therapies come to market. As such, we encourage ICER to rethink its thresholds through the lens of value and sustainability.

VIII. Conclusion

UCB respectfully appreciates this opportunity to comment and welcome further discussion with ICER. Please contact Amanda Ledford, Director of U.S. Public Policy, at Amanda.Ledford@UCB.com with any questions or feedback on our comments.

Sincerely,

A handwritten signature in black ink, appearing to read "Patricia A. Fritz". The signature is stylized and cursive.

Patricia A. Fritz
Vice President, U.S. Corporate Affairs
UCB, Inc.
770.970.8585 office
678.907.5867 mobile

ⁱ See Innovation and Value Initiative. Finding Equity in Value – Racial and Health Equity Implications of U.S. HTA Processes. [IVI Sick-Cells Equity-in-Value 2022.pdf \(thevalueinitiative.org\)](#)

ⁱⁱ Agboola F, Whittington MD, Pearson SD. Advancing Health Technology Assessment Methods that Support Health Equity. 2023.

ⁱⁱⁱ We did not perform a formal systematic review of methods in the literature or of practices of all international HTA bodies, although we did benchmark directly against the methods in use at the National Institute for Health and Care Excellence (NICE) in the United Kingdom, and the Canadian Agency for Drugs and Technology in Health (CADTH). We did not coordinate our efforts with other groups in the US embarked on similar efforts, including those organized by the Robert Wood Johnson Foundation, CMS, the Academy of Managed Care Pharmacy, and others. Additionally, although we worked closely with our Advisory Group, we did not publish a draft of this paper for public comment.

^{iv} See <https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trial-snapshot-ozempic>.

^v ICER's 2020 Revised Scoping Document Assessing Myasthenia Gravis Treatments.

^{vi} See Rand, Leah Z. and Aaron S. Kesselheim. Controversy Over Using Quality-Adjusted Life-Years In Cost-Effectiveness Analyses: A Systematic Literature Review. Health Affairs Vol. 40, No. 9. Sept. 2021.

^{vii} See [Will ICER's Response to Attacks on the QALY Quiet the Critics? - Center for the Evaluation of Value and Risk in Health \(tuftsmedicalcenter.org\)](#). Dec. 2018.

^{viii} See Innovation and Value Initiative. Proceedings report 2023, 4th Annual Methods Summit. [2023-Methods-Summit-Proceedings-Report FINAL.pdf \(thevalueinitiative.org\)](#).

ICER

2023 Value Assessment Framework Proposed Changes

Response to Call for Public Comment

Section 2. Comparative Clinical Effectiveness

On page 7, it states that the ICEMAN for RCT assessment tool will be used to determine the diversity of the study sample, but it is unclear whether subgroup analyses that do NOT include evaluation of effect modification will be considered (e.g., subgroup analyses conducted within single arm trials OR within other types of studies that do include comparison groups OR within real world implementation studies). If only subgroup analyses conducted within formal effect modification/moderation/interaction analyses will “count” towards the diversity rating using the ICEMAN for RCT criteria, then presumably all RCTs would need to be adequately powered to detect significant differences between groups?

In addition, on page 7, it states that “If the effect modifier is a continuous variable, were arbitrary cut points avoided?” Presumably, because the criteria include the age cutpoint of 65+ listed on page 4, this would not be considered as an “arbitrary cutpoint,” correct?

Section 3. Long-term Cost Effectiveness

Section 2 seems to require the conduct of RCTs to collect relevant evidence that will be assessed, however, it is unclear whether these types of study design requirements extend to studies of cost effectiveness (i.e., will any RWE studies or single arm trials with collected HEOR evidence be considered in the rating)?