

October 18, 2019

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

Dear Dr. Pearson:

We write representing patients and people with disabilities nationwide living with diverse conditions and diseases, as well as their families, caregivers and providers. We are pleased to provide feedback on ICER's proposed changes for its 2020 Value Assessment Framework.

Above all, we urge ICER to put patients and people with disabilities at the center of all of your assessments. While we share your interest in lowering healthcare spending and addressing affordability, ICER's use of discriminatory methods in its value assessments gives insurers tools to restrict patient access, an unethical tactic that puts the most vulnerable at an increased risk of worse health outcomes, increased out-of-pocket costs associated with their care, and potential adverse events. ICER's value assessments do not promote affordability for patients, but instead give payers justification to create barriers to treatment coverage that benefit their own bottom line. Yet, when patients are treated first with the right treatment for their individual condition, they are more likely to adhere to treatment, become healthier, and holistically save the healthcare system money.

Therefore, we echo our initial comment letter by encouraging ICER to align with innovative leaders in the field of patient engagement and value assessment. When Congress authorized the Patient-Centered Outcomes Research Institute (PCORI), it created a blueprint for engaging patients and people with disabilities throughout the research process to reflect real-world considerations for decision-making. Similarly, the Food and Drug Administration (FDA) has made tremendous progress with patient-focused drug development to identify outcomes that matter to patients and drive innovation to address them. Others in the private sector are following suit to advance patient-centered methodologies for assessing the value of treatments.

With this in mind, we appreciate your considering the following comments on your proposed changes.

ICER continues to defend the use of the QALY and other metrics that treat patients as averages when it should abandon these metrics and focus on development of novel measures of value to account for patient differences and priorities.

In its proposed changes, ICER indicated a commitment to multiple cost-effectiveness outcomes, but remains wedded to the QALY and equal value of life-year gained (evLYG), which treat patients as averages and do not account for heterogeneity in patient populations. We would like to strongly reiterate our criticism of the QALY and reinforce that the evLYG does not sufficiently reform this fundamentally flawed metric.

As we have stated consistently, QALYs discriminate against patients and people with disabilities by placing a lower value on their lives and insufficiently accounting for outcomes that they value. For this reason, the use of QALYs and similar summary metrics of cost-effectiveness have been disallowed for use in our public insurance programs. Medicare is prohibited by law from using a QALY-based threshold to determine coverage, and in 1992 the George H.W. Bush administration determined that state use of a QALY-based system to determine Medicaid coverage would likely violate the Americans with Disabilities Act.

QALYs also fail to properly represent health gain to a heterogeneous patient population. QALY weights are constructed in such a way that inadequately weights quality of life beyond the middle ranges.¹ They are also constructed by a very small subgroup of the country's population² and purport to represent 'all' when they ultimately represent no one.³ Considerable empirical evidence exists to demonstrate that technologies impact people to different degrees and that society strongly disagrees with treating all conditions, disease states, and patient types with the same priority.^{4,5}

This is not merely our perspective – it reflects the viewpoint of the largest analysis of the QALY's underlying assumptions: the European Guidelines for Cost-Effectiveness Assessments of Health Technologies, which concluded that "given the overwhelming methodological limitations of the QALY indicator, and the major inconsistencies which irrefutably invalidate its use, the use of QALY indicators should be abandoned for healthcare decision making."⁶

We would also like to reiterate the point made in our first comment letter on ICER's 2020 Framework that incorporating the evLYG does not resolve the QALY's flaws. While the evLYG partially mitigates the life-extension problem – if insurers use it – it still offers payers a means of refusing access to an effective and beneficial drug by using a summary metric that fails to account for outcomes that matter to patients. The evLYG does not address the challenges described above related to undervaluing quality of life improvements or ignoring clinical knowledge. A metric based on averages will never adequately reflect patient value, because there is no single perspective on how people see and value health. It is imperative that ICER consider the heterogeneity of patient populations, even within the same condition.

In addition, the evLYG's continued reliance on the QALY for evaluating quality of life improvements poses serious problems. The QALY's flaws are not limited to its underestimating of life-extension. It also fails to account for the full nuance in patient conditions when translating condition-specific measures into utility weights. For example, in ICER's analysis of esketamine,

¹ Smith S, Cano S, Browne J. Patient reported outcome measurement: drawbacks of existing methods. *bmj*. 2019 Feb 27;364:1844.

² McClimans L, Browne JP. Quality of life is a process not an outcome. *Theoretical medicine and bioethics*. 2012 Aug 1;33(4):279-92.

³ Broome J. Fairness versus doing the most good. *The Hastings Center Report*. 1994 Jul 1;24(4):36-9.

⁴ Weinstein MC. A QALY is a QALY is a QALY—or is it? *Journal of health Economics* July 1988 289-291.

⁵ Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *British medical bulletin*. 2010 Dec 1;96(1):5-21.

⁶ Echoutcome. European Guidelines for Cost-Effectiveness Assessments of Health Technologies. 2015, http://echoutcome.eu/images/Echoutcome__Leaflet_Guidelines___final.pdf

a new medication for treatment-resistant depression, ICER translated PHQ-9 scores, a condition-specific measure of depression, into QALY-based utility weights. This translation resulted in considerable lost nuance, since ICER took a measure (the PHQ-9) that ranged from 0 to 27 and simplified it into three health states: no depression, mild/moderate and moderate-severe/severe. As a result, significant improvements in health as measured by the PHQ-9 are assessed by ICER's model as delivering no value to patients due to the reliance on the QALY as the means of value assessment.

Instead of creating another problematic metric, the evLYG, that also does not capture the complexity of patient experience, we urge ICER to fully grasp the limitations of the QALY and invest in condition-specific metrics.

ICER's framework ignores ethical principles with broad support across the general public.

From an ethical perspective, valuing “perfect health” over pre-defined “less than perfect” states of health is fraught with issues. Indeed, our nation's constitutional foundation of equality and our public policies such as the Emergency Medical Treatment and Labor Act (EMTALA), a federal law that requires anyone coming to an emergency department to be stabilized and treated regardless of their insurance status or ability to pay, indicates our ethic to support patients and people with disabilities to maximize their individual potential for health.⁷ To define a life as less valuable because a person's unique circumstances deviate from “average” puts that American ethic at risk. An individual living with a chronic condition may be just as satisfied with their life as another individual with perfect health and should not be afforded less access to treatment.⁸

ICER's QALY-based approach reflects a strict utilitarian mode of thinking that contradicts the traditional American ethic that resources should be allocated to care for people with severe disabilities and chronic illnesses, as well as to research innovations that benefit them. While these groups may represent small portions of the population, the intensity of their need should not reduce their access to lifesaving medical care and reduce investment in research designed to develop innovative new technologies that may improve their outcomes.

Similarly, the QALY-based approach fails to afford patients the opportunity to make their own choices between conflicting priorities or to make tradeoffs. Often, different treatment paths will come with their own distinct benefits and disadvantages (which may manifest differently depending on the patient). The person-centered shared decision-making approach to care desired by most Americans allows patients the choice to select the treatment path most consistent with the values, needs and priorities for care relevant to their own lives. Unfortunately, the use of a QALY-based approach to set coverage decisions and prioritize certain drugs over others within a utilization management framework denies patients that decision-making authority.

⁷ Centers for Medicare & Medicaid Services. (2012, March 26). Emergency Medical Treatment & Labor Act (EMTALA). Retrieved 2017, from <https://www.cms.gov/regulations-and-guidance/legislation/emtala/>

⁸ Pettitt, D., Raza, S., Naughton, B., Roscoe, A., Ramakrishnan, A., Davies, B., . . . Brindley, D. (2016). The Limitations of QALY: A Literature Review. *The Journal of Stem Cell Research & Therapy*, 6(4).

ICER’s proposed crosswalk between ICER evidence ratings and the German HTA system is unrealistic and irrelevant.

We question both the relevance and validity of providing a crosswalk between ICER evidence ratings and those of the German health technology assessment (HTA) system. The ICER process is largely a statistical review of evidence from the population perspective. Its evaluation of evidence is primarily based on network meta-analysis, and its sole measure of the quality of evidence is statistical certainty.

By contrast, Germany’s Institute for Quality and Efficiency in Health Care (IQWiG) evaluation takes a different approach, which does not as heavily rely on statistical evaluation. Despite key differences between the ICER and IQWiG approaches, both in types of data, methodology, perspective and categorization, ICER believes these two can be simply translated from one to the other. This seems highly unrealistic and ICER does not offer a specific methodology for doing so. It is unclear why ICER is motivated to make this awkward crosswalk.

We support ICER’s recognition of the importance of real-world evidence (RWE) and implore it to incorporate RWE in its base models to ensure they carry real-world validity.

We applaud ICER for recognizing the importance of incorporating real world evidence. In the past, there have been numerous occasions in which ICER’s estimates of value were significantly flawed due to its over-reliance on randomized clinical trials (RCT) and inappropriate cohort data for estimates of underlying disease burden.⁹

As ICER makes this important change to support and use RWE, we encourage a comprehensive approach to ensure ICER’s reports more accurately represent value to the patient. In this spirit, it is essential that RWE is used in actual model input data. Since the aim is to assess the value of a new technology for actual patients in the real world, RWE is clearly a better source than RCTs, which generally include an unrepresentative subtype of young patients without comorbidities or diversity of backgrounds and ethnicities.

It should also be noted that even if ICER does make a committed effort to better incorporate RWE into its models, the value of this effort will be limited if it continues to undertake its reviews so early in the development process; often long before comprehensive RWE is available to be incorporated into models. RWE sources should be prioritized over RCT data for most inputs, including baseline risk, disease burden, cost data, scope, make-up of likely beneficiaries, and health-related quality of life data. If ICER continues to undertake reviews of drugs for which prices and indications are yet to be finalized, during a period when quality of life data are yet to be published, then this effort could be futile, failing to achieve real-world validity in its modeling that can be appropriately translated into a value determination for real people with a disease, chronic condition or disability.

We urge ICER to incorporate patient input meaningfully throughout the entire review process versus the ceremonial nod of summarizing their input.

⁹ Toth PP, Stevens W, Chou JW. Why published studies of the cost-effectiveness of PCSK-9 inhibitors yielded such markedly different results. *Journal of medical economics*. 2017 Jul 3;20(7):749-51.

Though ICER plans to include a separate chapter on the patient experience, we have concerns that this is only a ceremonial nod toward patients versus actually incorporating important patient reported outcomes in the base models of the reports.

If ICER is serious about developing its reports through the patient lens of value, then it should rely on condition-specific preferences of health-related quality of life (HRQOL) versus the QALY in its reports. Furthermore, a summary of patient input in the larger report is insufficient. We would advise that ICER not just summarize the input from patients but share their comments publicly at each stage of the process. Stakeholders have the right to hear directly from patients, not ICER's summation of patients' input. Summarizing lends itself to the omission of items deemed unimportant but may be seminal to patients. Additionally, ICER's summaries do not capture the volume of stakeholders that may have signed one letter related to their views and concerns but represent more than one voice.

We urge ICER to develop a mechanism for incorporating more robust clinician input, particularly when dealing with rare disease populations and want to express concern about the elimination of a higher threshold for treatments for ultra-rare diseases.

One of the biggest challenges facing people with rare diseases in value assessment is the difficulty in developing a research literature for a patient population that may number in the thousands or even hundreds. For such groups, essential information on patient subgroups and variation in medication efficacy and side effects may exist only among clinicians, since the patient population is not large enough to develop a sufficient research literature to meaningfully inform value assessment.

If ICER wishes to offer an honest assessment of value for orphan drugs, they must incorporate clinicians who specialize in serving the patient populations under discussion into the value assessment process.

We also want to express our concern about the elimination of the higher threshold for ultra-rare diseases. There is great need for treatments for rare conditions and disease populations are too small for ICER to evaluate effectively, relying as heavily on RCT data as it currently does. ICER risks limiting access to the populations that need them most based on methodologically flawed reviews. It is also concerning that, based on ICER's description of this change, it is being made solely with the goal of sending a message to manufacturers, not looking out for patients' best interests. ICER states that one of the primary reasons for the change is so that manufacturers do not believe that ICER has formalized \$500,000 per QALY as an appropriate cost-effectiveness threshold for treatments for ultra-rare conditions¹⁰. This stated goal callously overlooks the fact that 95% of rare diseases lack an FDA-approved treatment¹¹. Given that reality, the goal of ensuring that patients are able to access new treatments for these conditions should be prioritized above slapping manufacturers' wrists, and it is concerning that ICER fails to understand this.

¹⁰ Institute for Clinical and Economic Review, 2019. 2020 Value Assessment Framework Proposed Changes. August 21, 2019.

¹¹ Global Genes. Rare Facts. Accessed October 8, 2019.

ICER should allow for appropriate disease specialists and disease-impacted patients to serve as voting members for all reviews.

In order to accurately assess treatments for any condition it is imperative you have clinical specialists in that condition and patients who are living with it at the table.

The diseases for which ICER evaluates treatment are complex and there is a substantial amount of nuance surrounding their treatment. In order to ensure that best practices and the most up-to-date literature for treatment of these diseases is captured, it is imperative to incorporate the views of clinicians who are experts in the disease. As the Headache and Migraine Policy Forum noted in their initial letter on the 2020 Framework, during the 2018 ICER Migraine Review the voting panel initially included an OBGYN as the clinician expert. *After serious concerns were raised by the migraine community, this expert was finally supplanted by a neurologist.* Medical students typically undergo one hour of education on all topics related to neurology, which is an insufficient amount of training to fully understand the content of the review. This is one example of a pervasive problem within ICER reviews. In order to truly understand the nuance of a disease and its treatment ICER must include clinicians that are experts in the disease state.

ICER also consistently overlooks outcomes that matter to patients, such as respiratory function in the Duchenne Muscular Dystrophy Assessment. By incorporating patients as equal voting members, ICER would ensure that outcomes that truly matter to patients are being factored into their overall assessments.

We support ICER’s decision to re-evaluate evidence one year after each final report, but we continue to implore ICER to set more stringent standards for minimum data requirements for reviews and to cease conducting harmful premature reviews.

We continue to urge ICER to cease conducting premature reports and to wait until adequate data is available to produce more accurate and scientifically rigorous reports. ICER notes that “...(ICER) strongly believe(s) that such value assessments need to be conducted around the time of launch, to allow policymakers to make coverage and treatment decisions based on the best information available at the time.”

This statement relies on the assumption that inadequate data is more helpful or more informative than no data at all. Having significant numbers of insurers or providers limit access to new technologies due to flawed or incomplete data on value will impose costs in terms of the delayed health gains to patients.¹² Currently, ICER sees itself as the protector of the healthcare purse, providing payers flawed information to excuse restricted coverage at the expense of patients and people with disabilities. There must be a strong case for delaying access to new medicines, not just a justification not to spend, and it must be based on the best data available. It is inhumane and unethical for ICER to take the stance that we must save money first and overturn decisions on restricting access only when value has been proven, while patients suffer in the interim.

¹² Stevens W, Philipson T, Wu Y, Chen C, Lakdawalla D. A cost-benefit analysis of using evidence of effectiveness in terms of progression free survival in making reimbursement decisions on new cancer therapies. Forum for Health Economics and Policy 2014 Jan 1 (Vol. 17, No. 1, pp. 21-52).

Expanding on this, given ICER's practice of undertaking many of its reviews far too early - often when there is inadequate data available to make realistic estimates of value - we agree with and support ICER's proposal to re-evaluate evidence one year after the release of each final report. The existence of time-variance as a driver in cost-effectiveness is very much an issue that is being discussed in academic circles. We would hope, given the prematurity of many of ICER's initial reports, that ICER puts as much emphasis on its newer results and updates to initial reports as it does to its primary report launches. Later reports will likely be more accurate than the early reports and should be emphasized.

ICER has chosen to give itself eight more weeks for large class reviews while passing a one week extension on to patients. If ICER actually values meaningful input from stakeholders, especially patients, comment periods must be extended.

Over the years ICER has heard from the Partnership to Improve Patient Care and many other patient groups that they allow insufficient comment periods. Advocacy organizations have tremendous depth of knowledge and information to share on the real-world value of treatments, yet often have few resources to dedicate to ICER's process. Meaningful patient engagement requires longer comment periods for patients to develop thoughtful and substantive input. Though ICER has proposed elongating its timeline by nine weeks for large class reviews, only *one* of those weeks is being added to the comment period. This follows ICER's concerning pattern of short-changing the patient voice by not allowing time and resources for patient advocates to fully engage. If ICER is serious about valuing patient input, extensions should be granted to both comment periods equivalent to the time extension ICER is giving itself.

As ICER looks to apply more precise evidence ratings, it is imperative that this is implemented in a manner that reflects a real-world setting and heterogeneous patient population.

External validity should be ICER's primary focus in cost-effectiveness analyses. ICER cannot improve upon the internal validity of a clinical trial *ex ante*, so its sole purpose is to ensure that such evidence can be applied with relevance to a wider audience. ICER's reports seek to instruct general medical practice and policy in a world where there is no 'controlling' of selection of subject.^{13, 14}

Given the clear difference in importance of internal and external validity for producing value assessments, we would suggest that evidence ratings be undertaken separately for both internal and external validity and also extend beyond simple 'effectiveness' to other sources of input data used in comparative effectiveness models such as cost data, real world burden, real world risk, transition probabilities between health states, and quality of life data.

¹³ Glasgow RE, Green LW, Klesges LM, Abrams DB, Fisher EB, Goldstein MG, Hayman LL, Ockene JK, Tracy Orleans C. External validity: we need to do more. *Annals of Behavioral Medicine*. 2006 Apr 1;31(2):105-8.

¹⁴ Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *Jama*. 2016 Sep 13;316(10):1093-103.

We would also suggest implementing evidence ratings of effectiveness that concentrate not just on selection bias, uncertainty and reliability but also measures of heterogeneity. Although ICER states clearly in this document that it takes a ‘population’ perspective to evidence (lines 360-373), we strongly recommend that ICER also acknowledge that the average does not represent all.

In ICER’s published assessments, the issue of heterogeneity has not been featured strongly in the reports of the main clinical results. In its cost-effectiveness analyses, heterogeneity is only addressed post-hoc after the main model has been built. ICER’s Evidence Rating Matrix makes no mention of whether a study attempts to detect or understand heterogeneity or to report results by subgroup. It is imperative that ICER recognize the importance of evidence on heterogeneity as it has been well established that reporting of differential value assessment across subgroups will lead to substantial health gains, both through treatment selection and coverage.^{15, 16, 17}

ICER states that when dealing with particular individuals, “*decisions will be made with other sources of data in mind.*” The problem is that with increasing evidence of genetic and epigenetic impacts on relative effectiveness of different therapies as well as the growing importance of personalized medicine in the health care industry, ignoring heterogeneity will result in providing evidence that is relevant for no one, rather than relevant for everyone.

Conclusion

Thank you for your consideration of our suggestions on ways in which ICER can make its value assessments fair and equitable to patients. Please feel free to reach out to Sara van Geertruyden (sara@pipcpatients.org) in response to our recommendations above.

Sincerely,

ACCSES
Aimed Alliance
Alliance for Aging Research
Alstrom Syndrome International
American Association on Health and Disability
American Autoimmune Related Diseases Association
Association of Migraine Disorders
Association of University Centers on Disabilities
Asthma and Allergy Foundation of America
Beyond Type 1
Bridge the Gap -Syngap – Education and Research Foundation

¹⁵ Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered healthcare. *Journal of Health Economics* 2011; 30(3): 549-559.

¹⁶ Basu A, Jena A, Philipson T. Impact of comparative effectiveness research on health and healthcare spending. *Journal of Health Economics* 2011; 30(4): 695-706.

¹⁷ Espinoza MA, Manca A, Claxton K, Sculpher MJ. The value of heterogeneity for cost-effectiveness subgroup analysis: conceptual framework and application. *Medical Decision Making*. 2014 Nov;34(8):951-64.

CancerCare
CARE About Fibroids
ClusterBusters
Cystic Fibrosis Research, Inc. (CFRI)
Diabetes Patient Advocacy Coalition
Epilepsy Foundation
Epilepsy Foundation New England
Genetic Alliance
Global Healthy Living Foundation
Global Liver Institute
GO2 Foundation for Lung Cancer
GoldenGraine
Heart Valve Voice US
Hope for Migraine Community
Institute for Patient Access
International Foundation for Autoimmune & Autoinflammatory Arthritis
Lakeshore Foundation
Lupus and Allied Diseases Association, Inc.
LymeDisease.org
Men's Health Network
Mended Hearts
Miles for Migraine
MLD Foundation
National Alliance on Mental Illness
National Diabetes Volunteer Leadership Council
National Headache Foundation
National Infusion Center Association
Not Dead Yet
Partnership to Improve Patient Care
Preventive Cardiovascular Nurses Association
PXE International
Rosie Bartel
Sick Cells
SoldierStrong Access
The Bonnell Foundation: Living with Cystic Fibrosis
The Coalition For Headache and Migraine Patients
The Headache and Migraine Policy Forum
The Migraine Diva
Tuberous Sclerosis Alliance
U.S. Pain Foundation
United Spinal Association