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

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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.

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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 (FEV_1) 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.[4][5] 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.

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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 FEV_1. 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.

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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.

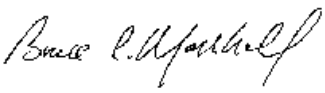
While the Foundation recognizes why ICER separates this section due to the lack of quantifiable data, we have concerns that, by separating these inputs, this data is not given appropriate weight within the report. We urge ICER to consistently incorporate these benefits into the report in a standard way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

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