CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

October 21, 2019

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

Re: Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Draft Background and Scope

Dear Dr. Pearson,

On behalf of the 30,000 individuals living with cystic fibrosis (CF) in the United States, we write to provide public comment on the *Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Draft Background and Scope*. We appreciate the opportunity to help incorporate the patient and clinical perspectives during this process.

Modulators mark a significant advancement in the treatment of cystic fibrosis.
Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that result in the absence or malfunction of the CFTR protein. Decreased CFTR function causes progressive pulmonary and gastrointestinal disease that result in early death, usually by respiratory failure.

CFTR modulators, a class of CF drugs which encompasses the four drugs in this proposed scope — ivacaftor monotherapy, lumacaftor/ivacaftor combination therapy, tezacaftor/ivacaftor combination therapy, and elexacaftor/tezacaftor/ivacaftor triple combination therapy — are designed to correct specific defects in the CFTR protein. Modulators are the only treatments available that address the underlying cause of CF rather than alleviating the symptoms or addressing clinical manifestations of the disease. Modulator therapies are mutation-specific because different mutations lead to different defects in the protein. Research is rapidly evolving in this therapeutic area and has presented tremendous opportunity for new and existing modulators to benefit individuals beyond those currently indicated.

The scope of this review should be narrowed to elexacaftor/tezacaftor/ivacaftor.
The CF research community has continued collecting and publishing additional studies on the long-term impact of these drugs on patients eligible to take them. However, it is unlikely these additional data will significantly change ICER's findings from last year on ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor. We recommend focusing the scope of this review on the new elexacaftor/tezacaftor/ivacaftor triple combination therapy.

Further, in the absence of data outside the clinical trial for the triple combination therapy, we advise reviewers to focus on studies of ivacaftor to best understand the long-term outcomes patients are likely to experience on elexacaftor/ivacaftor/tezacaftor. These two treatments can both be considered "highly effective modulator therapies" (HEMTs) and thus ivacaftor is the closest comparator to the triple combination modulator.

ICER should consider reviewing elexacaftor/tezacaftor/ivacaftor using the ultra-rare condition framework.

The scoping document asserts that the triple combination therapy "has the potential for use in 90% of all patients with CF." To clarify, the introduction of the triple combination therapy to market will increase the number of people with CF benefitting from a HEMT to approximately 90%. However, not all of these individuals will be eligible for or prescribed the triple. The CF Patient Registry can be used to help estimate eligible populations.

It is also important to recognize the initial Food and Drug Administration (FDA) label for elexacaftor/tezacaftor/ivacaftor is limited to persons 12 and older.

Intervention and comparison populations that are heterozygous for the *F508del* mutation and residual function mutation must be clarified.
In both the Intervention and Comparative Analysis sections, the document notes that Population 3 (people with CF who are heterozygous *F508del* and residual function mutation) will be eligible for all four modulators. This is not correct. This population is not eligible to take lumacaftor/ivacaftor based on the FDA label. ICER should remove lumacaftor/ivacaftor from the scope of the analysis for this population.

Additionally, for Population 3, ICER states that the analysis will use "reasonable assumptions" to model the triple combination therapy. Please define what assumptions will be used in this modeling. As stated earlier, we recommend focusing on studies of ivacaftor monotherapy to reflect the long-term outcomes patients will likely realize on the triple combination modulator.

Please clarify how evidence will be used within the comparators section.
The scope of this review indicates ICER will potentially utilize studies outside of randomized control trials (RCTs). Please define how reviewers intend to address confounding by indication: specifically, for the cases where those who are prescribed a modulator are less healthy than those not prescribed the therapy.

Consider updating the Outcomes section.
We propose adding sweat chloride as an intermediate outcome as it is directly associated with many of the key outcomes identified. Further, please clarify what health-related quality of life measure will be used; we recommend using the CFQ-R respiratory domain, a validated instrument for use in cystic fibrosis.

Consider removing liver transplant from the Other Outcomes as it is a rare event: there were 22 patients with CF that received a liver transplant in 2018.[i] Within this same section, we appreciate the recognition that patient-reported outcomes and patient experience data are important components of value. However, we reiterate our comments from previous letters that ICER is conducting this review without ample long-term or patient experience data for several of these drugs. Given that data collection is still underway, ICER should recognize and note in the assessment that there will be significant limitations in this analysis.

Liver function and injury should be added to the Adverse Events list as modulators have the potential to negatively impact the liver. There is no current data on the impact of the triple combination therapy on liver function. Nevertheless, we recommend this adverse event be included in the analysis due to the potential impact on people with CF.

Finally, we recommend the following wording changes to improve the clarity of the following outcomes:

- *Pill burden and correlation to adherence with medication regimen*: we recommend changing this to "treatment burden," perhaps in hours or minutes per day. Daily CF treatment not only includes a number of pills, including pancreatic enzyme replacement therapy with every snack and meal, but also nebulized treatments and airway clearance therapy. Of note, treatment burden can also include the time spent cleaning and maintaining devices. For example, components of nebulizers must be changed after each use.
- *Pseudomonas colonization:* we recommend changing this to "Pseudomonas infection."

The analyses would be strengthened with the inclusion of additional scenarios.
Given the progressive nature of CF, the point at which a patient initiates modulator therapy can significantly impact clinical outcomes realized by that patient. For example, ivacaftor can be taken by children as young as 6 months old (prior to the development of lung disease and possibly prior to the development of irreversible pancreatic dysfunction) whose disease will not have progressed as much as an adult with the same mutation. We recommend including additional scenarios beyond the lifetime time horizon model that better reflect this.

We appreciate ICER's use of measures other than the QALY to quantify benefit.
The use of quality-adjusted life-years (QALY) as the primary measure of the cost-effectiveness analysis is concerning as QALYs do not account for patient-reported outcomes. We appreciate that ICER will acknowledge such limitations under the framework for ultra-rare diseases and is incorporating the equal value life years gained (evLYG) as an additional effectiveness measure.

Identifying low value services
We appreciate ICER's interest in identifying low value services in CF care that arise from modulator treatment. Clinical guidelines developed by multidisciplinary and independent committees[ii] provide population-level guidance on respiratory, nutrition and GI, modulator use, and other areas of CF care. Modulator therapies are currently intended to complement existing best practices, but CF Patient Registry data shows that some standard-of-care therapies have been discontinued. To keep up with the evolving treatment landscape, randomized and real-world withdrawal studies are underway or being planned to evaluate the feasibility of withdrawal or possible changes to the current CF care regimen.

Thank you again for the opportunity to bring the CF clinical and patient community perspective forward during this review process and the chance to provide comment on *Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Draft Background and Scope*. Please contact Lisa Feng, DrPH, Senior Director for Policy & Advocacy, with any questions or concerns at lfeng@cff.org.

Sincerely,

Mary B. Dwight
SVP, Policy & Advocacy

Bruce C. Marshall, MD
SVP, Clinical Affairs

[i] 2018 Patient Registry Annual Data Report, Cystic Fibrosis Foundation. Bethesda, MD.
[ii] Sponsored by the CF Foundation