PATIENTS RISING NOW

December 11, 2020

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

RE: Draft Evidence Report "Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD"

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with serious and chronic conditions and diseases for them to have access to life-improving and life-saving therapies and services. Access to such treatments and services is essential, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers, and others to foster people-centered discussions about the entire U.S. health care system. Our goal is a balanced dialogue that illuminates the truth about health care innovations and advancements in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's November 12th Draft Evidence Report, "Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD." Our comments about the draft report are organized below into sections about People-Centered Perspectives; Modeling and Projections; Uncertainties and Assumptions; and Additional Points.

People-Centered Perspectives

Clearly, high cholesterol is a serious medical condition that can lead to many extremely consequential health problems that impair quality of life and may lead to early death. That is why treatment of high cholesterol and ASCVD is very important, and shared clinical decision-making between a patient and their care team is critical. We also note that awareness of high cholesterol is a public health matter, which is why people are encouraged to "know their heart numbers" including cholesterol along with blood pressure and body mass index.

As you know, as awareness has increased that blood cholesterol levels as a risk factor for cardiovascular disease (CVD), more treatment options have been developed – from sequestrants to statins to PCSK9 inhibitors and others. And of course, diet and exercise are also clearly important for helping control risks of CVD.

We include of this background information because there are many facets and perspectives about cholesterol and ASCVD and its treatments that are important to people, but which are either scarcely mentioned or entirely missing from ICER's extremely myopic draft report. Below are some points that we strongly believe ICER should expand upon in the next version of the report, and absolutely must include as part of the discussion at ICER's committee meeting:

- The draft report notes that women with familial hypercholesterolemia are less likely to reach LCL-C treatment goals.[i] This is completely consistent with the well-known sex differences in the symptoms and presentation of heart disease, its diagnosis, and for some treatments.[ii] There is also a tendency to think of heart disease as a "man's disease," creating a systemic – if unintentional – systemic bias against female heart disease patients in the U.S. health care system. Such bias is also evident in ICER's draft report where it summarizes the Ballantyne 2020 study by characterizing the participants as "50% were male." However, the actual published report[iii] clearly states that "50.5% of patients were women," and the word "male" appears nowhere in the publication. It is improper and misleading for ICER to ignore the known real-world sex differences in heart disease. We strongly suggest that ICER evaluate its own perspectives and biases, and address this issue in the next version of the report and in ICER's committee discussions.
- Diet, exercise, and smoking cessation – as well as treating other conditions such as diabetes mellitus – contribute to prevention of CVD outcomes such as myocardial infarction, heart failure, peripheral vascular disease, amputations, sexual dysfunction secondary to vascular insufficiency, and stroke. The draft report lumps those factors together into the catch-all "risk factor modification"[iv] without exploring the importance of addressing any of them individually or collectively via comprehensive patient-centered medical care (outside of biopharmaceutical treatments), or the importance of doing so for improving the lives and clinical outcomes for people with high cholesterol and CVD.
- The draft report contains extremely limited information about quality of life (QoL). This may be due to the limited number of clinical trials ICER relied upon as input for this draft report, which themselves contained limited assessment of QoL. Regardless, we strongly feel that even if specific metrics of QoL were not included in those studies, ICER should note the lack of those metrics, discuss other sources of information about the QoL implications of CVD and various treatment options (including diet and exercise), and propose how to fill that data void going forward. Similarly, we noted that in the description of the Midwest CEPAC's role that QoL is not part of their mandate from ICER: "The Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve **the quality and value of health care"** (emphasis added).[v] We see it as unethical for ICER's committees to omit QoL factors and perspectives from their stated core mandate and urge ICER to update the committee's focus and responsibilities. We are particularly concerned about this lack of attention to QoL because toward the end of the discussion of the uncertainties about the model created for the draft report, it is stated that the model "does not assume any permanent quality-of-life reduction from recurrent [Major Adverse Cardiovascular Event] of the same type as prior events."[vi]
- The draft report states: "Access to new therapies was of particular concern to patients, given the often-cumbersome insurance prior authorization process for newer cholesterol-lowering drugs like PCSK9-inhibitors and has resulted in delayed or denial of access to therapy for some patients." And further, "Patient groups and clinicians noted that insurance type and status may also play a role in uptake of therapy in part due to anticipated insurance challenges for new therapies based on experiences with the prior authorization process with PCSK9 inhibitors."[vii] Rather than just repeat what patients and clinicians have said, ICER should discuss how its own reviews contribute to this challenge, as they are used by insurance companies to justify access barriers that prevent patients from receiving treatments recommended by their clinicians.

- Supporting the previous point is the evidence cited in other ICER reports about PCSK9 inhibitors about access and affordability problems for patients. Specifically, in 2017, ICER found that only 17% of prescriptions for PCSK9 inhibitor medicines were being initially approved (with another 26% approved after appeal), and 25-40% of patients did not fill their prescriptions – presumably because of insurance company cost-sharing requirements.[viii]
- ICER's prioritization of economic factors and insurance company policies is also evident in how the draft report is structured, with Coverage Policies[ix] – which are based on economic considerations – being presented ahead of Clinical Guidelines[x] – which are based upon scientific and medical evidence. We suggest reversing the order of those sections to reflect a more appropriate prioritization.

Modeling and Projections

The draft report contains an extremely complicated modeling scenario using an almost countless number of assumptions – many of which are based upon divergent sources that may or not be applicable for the populations and treatments that are the subject of the draft review.

Beyond that complexity and extreme uncertainty based upon various assumptions, we note that the projections fail to recognize the possibility of future developments in the treatments for high cholesterol. Specifically, the draft report assumes the FDA will approve inclisiran, but there is no mention of other potential treatments that may be undergoing advanced clinical testing and could also be approved for use in the next few years. Additional treatment availability would dramatically affect the budget impact assessment that ICER has already split between inclisiran and the bempedoic acid medicines. We are highly confident that ICER could evaluate that pipeline based upon information from ClinicalTrials.gov, public disclosures from companies, analysts' reports, and projected PDUFA dates and windows. Clearly no modeling of this type would be perfect, but we recognize that ICER's standard practice is to do reports involving limited data, including about compounds undergoing FDA review – some of which later do not get approval as expected. Given that ICER regularly bases its models and projections on yet-to-happen events, this would seem to be completely within ICER's capabilities, and we see no reason why ICER should not model – and project – as accurate a picture of the future as possible.

Similarly, for the long-term cost-effectiveness modeling, we strongly recommend that ICER include cost calculations based upon the expected competition from generic and biosimilar versions of the two compounds reviewed in the draft report. While it could be argued that it is uncertain as to when that competition will occur, rather than viewing the future world as essentially static, ICER should adopt realistic perspectives factoring in those significant cost reductions. Consistent with that real-world understanding, we note that ICER presented updated reviews for the PCSK9 inhibitor medicines in 2017[xi] and 2019,[xii] which included reductions in costs based upon lower net and list prices. Although we are puzzled that ICER did not use net prices in both cases, even if that net price had to be estimated rather than based upon specific data sources – particularly since Medicaid, Medicare Part D and the Veterans Administration receive specific minimum discounts off of the list prices. Therefore, using list price alone is knowingly presenting a fictional scenario.

Related to the utility of the budget impact projections, ICER states that those projections are to potentially "trigger **policy actions** to manage access and affordability" (emphasis added)."[xiii] Again,

this assertion assumes a monolithic, uniform health care payer system in the United States, rather than the reality that there are a number of different – and sometimes overlapping – payers and care providers, such as Medicare, the VA and HMOs, each of whom has different populations, legal and regulatory obligations, and abilities, and hence different abilities to enact "policy actions" that would restrict patients' access to treatments, or influence the organization's or individual patient costs.

Uncertainties and Assumptions

The draft report summarizes and attempts to analyze the clinical trial data for two experimental treatments. While the draft report contains a little over one page about "Uncertainties and Controversies,"[xiv] other parts of the draft report are littered with mentions of the various assumptions that are made in taking data from a variety of sources and using it to numerate aspects of potential real-world situations. Such cherry-picking of data from controlled trials and scientific studies leads to serious questions about the applicability of such quantitative outputs to real world situations and care decisions. The draft report touches upon this absurdity with this statement: "Our goal was to examine the cost-effectiveness of these novel lipid-lowering therapies in real world populations, assuming that the efficacy observed in clinical trials would be replicated and sustained in clinical practice."[xv]

One particular assumption in the draft report that we want to highlight is: "[W]e assumed that the age-specific non-CV mortality in this cohort was similar to the general US population."[xvi] While the draft report cites a CDC dataset, it is a broad, and dramatic assumption considering that people with CVD may have risk factors (e.g., diet, exercise, and smoking) that would put them at increased risk for other conditions, such as cancer. ICER should explain its justification for this assumption and the CDC's WONDER database is used.

Additional Points

- The data report for Ballantyne 2020 in the text is incorrect when it states that "63% had HeFH"[xvii] and in Table 4.1 where it lists "ASCVD: 62.5%"[xviii] The correct citation of the data from the publication is "62.5% of patients had ASCVD and/or HeFH."[xix]
- In the discussion of the methodology for the Potential Budget Impact we note that these calculations are intended to be "aligned with the overall growth in the US economy."[xx] Given that the US and global economies have been extremely hard hit by the COVID-19 pandemic, significantly challenging companies projecting and reporting their financials as required by the Securities and Exchange Commission[xxi] – ICER should explain how it has developed its insights for the "growth in the US economy," particularly if it is relying on projections that predate the COVID-19 pandemic.
- The draft report states that the Midwest CEPAC is "an independent committee of medical evidence experts from across California," however, according to ICER's website with information about Midwest CEPAC, none of the members are from California. Similarly, the list of acronyms lists "CTAF California Technology Assessment Forum," which we find referenced nowhere else in the draft report.
- In Section 4 of the draft report ("Comparative Clinical Effectiveness"), the name implies that the two compounds that are the focus of the draft report are actually compared to one another directly. However, as the draft report notes, no such comparisons were made, and the review was conducted using a meta-analysis; thus the results are associative rather than directly comparative. Therefore, we strongly suggest that the title for this section be "Associated Relative Clinical Effectiveness" or "Indirect Clinical Effectiveness Associations."

- The draft report uses both "quality of life" and "quality-of-life." ICER should pick one and be consistent.
- The draft report uses both "healthcare" and "health care." We've previously expressed a preference for "health care," but ICER should pick one and use it consistently.

Conclusions

Patients Rising Now agrees with the draft report's summation: "The arrival of two new lipid-lowering therapies expands the therapeutic options available to patients with established ASCVD. This is a welcome development, given that this high-risk group of patients continues to experience recurrent CV events despite optimal therapy with statins and ezetimibe."[xxii] However, beyond that, we find the draft report lacking in many substantive and technical ways, including lack of attention to quality of life, and reliance upon so many assumptions and uncertainties that the numerical reported results are highly suspect and questionable. Overall, the draft report is very un-person-centered, and appears aimed at justifying insurance companies' erecting access restricting and affordability barriers – similar to what has occurred with other treatments for high cholesterol and cardiovascular diseases in recent years.

Therefore, we are concerned that based on the very limited data and perspectives in the draft report, access to current and future treatments for cardiovascular diseases may be limited by insurance plans through formulary, cost-sharing, or prior authorization schemes based on ICER's activities, which may at the same time expand administrative burdens for clinicians and patients.

Sincerely,

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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[i] Draft report, p. 1

[ii] https://www.womenshealth.gov/heart-attack, https://www.nhlbi.nih.gov/science/womens-health; https://www.womenheart.org/; https://www.cdc.gov/heartdisease/women.htm; and "Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR®) PINNACLE registry,": Thompson LE, Maddox TM, Lei L, et al., *J Am Heart Assoc.* 2017;6(7).

[iii] Reference #46 in the draft report: Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *European Journal of Preventive Cardiology.* 2020;27(6):593-603.

[iv] Draft report, p. 2

[v] Draft report, p. ii

[vi] Draft report, p. 81

[vii] Draft report, p. 10

[viii] "Evolocumab for Treatment of High Cholesterol: Effectiveness and Value" ICER New Evidence Update, September 11, 2017

[ix] Draft report, p. 12

[x] Draft report, p. 16

[xi] "Evolocumab for Treatment of High Cholesterol: Effectiveness and Value" ICER New Evidence Update, September 11, 2017

[xii] Alirocumab for Treatment of High Cholesterol: Effectiveness and Value" ICER New Evidence Update, February 15, 2019

[xiii] Draft report, p. 90

[xiv] Draft report, pp 39-40
[xv] Draft report, p. 46
[xvi] Draft report, p. 53
[xvii] Draft report, p. 22
[xviii] Draft report, p. 25
[xix] Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. European Journal of Preventive Cardiology. 2020;27(6):596
[xx] Draft report, p. 88
[xxi] https://dart.deloitte.com/USDART/home/publications/deloitte/financial-reporting-alerts/2020/financial-reporting-considerations-economic-downturn-covid
[xxii] Draft report, p. 81