NATIONAL FORUM
FOR HEART DISEASE & STROKE PREVENTION
1150 Connecticut Ave. NW, Ste. 300, Washington, DC 20036

August 20, 2019

Ms. Ellie Adair
Program Manager
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
Boston, MA 02109

Dear Ms. Adair,

The National Forum for Heart Disease and Stroke Prevention (the National Forum) is pleased to provide feedback on ICER's draft evidence report entitled "Additive Therapies for Cardiovascular Disease: Effectiveness and Value." We appreciate your willingness to review comments and recommendations from the National Forum's Value & Access Steering Committee and its partners (Steering Committee) working on these issues.

Cardiovascular disease (CVD) is the No. 1 killer of Americans and drives substantial human costs and other burdens on society. The Steering Committee is committed to building consensus among diverse stakeholders and reducing obstacles that patients living with CVD face in receiving the treatment that is right for them. Together, we strive to accelerate collaboration and improve access to evidence-based care.

The Steering Committee appreciates ICER's general conclusion that rivaroxaban (Xarelto®, Janssen) and icosapent ethyl (Vascepa®, Amarin Pharma), prescribed as additive therapies for CVD, confer gains in quality-adjusted survival and overall survival over optimal medical management, and that the costs for either treatment would fall below commonly cited thresholds for cost-effectiveness.

Our comments center on the guiding principles that (1) patients should have access to evidence-based, cost-effective treatments that are determined appropriate in consultation with their treating clinicians; and (2) cost-effectiveness analyses should be transparent and stakeholder-inclusive, remain within scope, and avoid commentary beyond the evidence base of the resulting analysis and conclusions.

Overarching Thoughts and Recommendations

- Icosapent ethyl and rivaroxaban are different products with distinct mechanisms of action that diverge in both FDA-approved indication and studied population. A "comparative" review presumes that it would be appropriate for clinicians considering one of these options for a particular patient to substitute the other as a more cost-effective option. ICER should clarify that by conducting separate analyses, it generated separate conclusions that each intervention meets applicable cost-effectiveness thresholds, and that the resulting report is not intended to guide clinical decisions ***between*** the products.

- Models of cost-effectiveness are helpful inputs to decision making, but their conclusions depend on the accuracy of the underlying assumptions. ICER's discussions of considerations beyond the scope of its cost-effectiveness inquiry, including flagging areas of uncertainty, speculating on potential combination therapy regimens, projecting adherence factors, etc., can have ramifications on patient access that are unwarranted and potentially harmful, and dilute the impact of ICER's primary conclusions. We believe any "unresolved" issues are better left in the capable hands of specialty societies, with individual patient decisions tailored to the patient's unique needs and circumstances. ICER reports should reduce or eliminate this content, and clearly flag any included statements or queries as beyond the scope of the cost-effectiveness report.
- Federal payers are moving toward value-based care and payment which join evidence-based guidelines with patient-centered care. Indiscriminate application of ICER's societal/payer perspective to pricing benchmarks has at times frustrated the goal of improved outcomes.
    - ICER's review of PCSK9 inhibitors presents an example of unintended, and extreme, impacts on patient outcomes. Although ICER's review may have pushed manufacturers to eventually reduce prices, patient access hurdles abounded during the intervening 4 years preceding pricing cuts. A recent study found sharply increased cardiovascular events among high-risk patients denied access to PCSK9 inhibitors.

Cost-effectiveness

Once again, the Steering Committee agrees with ICER's conclusions that both icosapent ethyl and rivaroxaban are clearly cost-effective in the populations studied within the draft report. The additional comments and recommendations expressed below are intended to both amplify ICER's cost-effectiveness conclusions on these treatments and help guide its inquiry and process for future evaluations of coronary artery disease (CAD) products.

- The Steering Committee was disappointed that ICER did not provide access to its model for public input until after presenting the draft conclusions derived from its use. Early and continuing transparency, combined with stakeholder input on what may be the most important driver in ICER's analyses, would improve model validity and enhance stakeholder acceptance of resulting reports.
- ICER stated that "CVD also imposes a substantial financial burden, with annual direct and indirect costs estimated to total $330 billion." This understates the total current and projected costs of CVD used to calculate cost-effectiveness and budget impact.
    - The 2010 direct-cost burden from CVD was $273 billion and is projected to rise to $818 billion by 2030.
    - 2010 indirect costs related to lost productivity/work/etc. were $172 billion and are projected to more than double to $276 billion by 2030.
- We continue to view QALY as an imperfect metric because it has potential for discrimination against those with baseline disabilities, comorbidities and advanced age, all of which are common in CAD patients;
- The Steering Committee urges ICER to consider factoring total major adverse cardiovascular events (MACE), as done in the clinical trials, into inputs and resultant analyses. In the real world, CVD patients have multiple events, each one carrying costs and other burdens that, if not captured holistically, can undermine the accuracy of cost-effectiveness estimates.

- ***Icosapent ethyl*** - Revascularization and unstable angina are important components of the 5-point MACE primary endpoint in REDUCE-IT but were not included as primary endpoints in ICER's evaluation. ICER used a 3-point MACE instead. This may have been due to ICER's interest in "comparing" data between the two treatments reviewed. This type of inter-study comparison cannot be made with scientific validity. Moreover, ICER used risk calculators in place of clinical trial data, to estimate, rather than count, event rates. We believe failure to consider the entirety of pivotal trial data reduces the accuracy (and evidence-basis) of cost-effectiveness calculations.
- ***Rivaroxaban*** – The Steering Committee strongly believes that comparison to DAPT is inappropriate and misleading. Presenting clopidogrel as a generic, cheaper alternative to rivaroxaban is misrepresentative. DAPT is indicated most often in patients with recent MI/CVA or ACS, *not* in the chronic population within rivaroxaban's indication.

Limitations in Data and/or Analyses Requiring ICER Transparency

- Women and minorities were underrepresented in both the REDUCE-IT population (<30% female and <10% persons of color) and the COMPASS population. Minorities are at greater risk of adverse CVD outcomes, and the burden of CVD is higher in minority populations.
- The draft report notes that "[t]he incremental benefit of adding either of these two treatments to current medical management relative to adding another relatively new treatment such as a PCSK9 inhibitor is unclear, as are the potential benefits of all of these agents in combination."
  - We reiterate our recommendation that ICER judiciously avoid commentary on issues and factors it was unable to examine within the scope of its report. Reports that blend evidence-based analysis with conjecture, speculation, and identification of uncertainty can have profound, unintended adverse impacts on patient access.
  - Without clear caveats explicitly separating this commentary from ICER's evidence-based conclusions, clinicians and payers could interpret these statements as cautions against specific uses.
- ICER's base-case analysis took a health care sector perspective and ignored productivity losses to the patient and caregiver. Although the draft report included a scenario analysis using a modified societal perspective, we are concerned that the overall burden of CVD is not fully incorporated into the draft report.
- The Steering Committee is concerned that ICER's mention of the STRENGTH trial studying carboxylic EPA+DHA injects confusion with respect to comparing the results of that study with REDUCE-IT. These are distinct drugs with different delivery mechanisms that are not suitable for direct comparison, much less speculative comparison. The study will likely run through the end of October 2019, with results expected in Spring 2020 and, while this study is expected to be informative, we do not view it as impacting any conclusions derived from the REDUCE-IT study.
- Real-world use:
  - It is unclear how ICER approached medication adherence in its ultimate analysis and assessment given the seemingly conflicting statements in the draft report. (see below). We urge ICER to avoid projecting adherence issues onto new, cost-effective products, or providing commentary that is more appropriately vested within the practice of medicine.
    - ICER noted that "[w]e also heard that medication adherence might be a challenge in this population, given already high rates of polypharmacy and comorbidity in older patients likely to be candidates for add-on therapy." This factor ostensibly cuts against the "value" of the treatments.

- Elsewhere, the draft reported stated that "[b]ecause both agents represent new mechanisms of action, they represent important treatment options that may be complementary to existing treatment mechanisms (e.g., PCSK9 inhibition), and may offer benefit if adherence to existing treatment is sub-optimal.

Budget Impact

The Steering Committee has significant concerns that the "Budget Impact" portion of ICER's draft report represents a health care rationing framework that detracts from the overall usefulness and public acceptance of ICER's cost-effectiveness work. ICER's use of finite fiscal thresholds in assessing budget impact skews unfavorably against any intervention for a common condition, regardless of the severity of the condition or the cost-effectiveness of the intervention. For example, in the case of icosapent ethyl, this framework implies that the price of drug would have to be similar to what patients pay for ordinary, low-cost OTC medications treating colds or seasonal allergies for all appropriate patients to have access. While clinicians, payers, and patients may have divergent perspectives in defining value, there is little disagreement over whether patients who might benefit from a cost-effective treatment should have access to it.

We believe that ICER would be more effective and avoid contributing to barriers for patients needing life-saving medications, if it remained focused on the longer-term CE analyses relevant to value and did not venture into short-term budget impact analyses. We note that:

- ICER's most recent reports give rise to serious concern that products for rare life-threatening diseases will never clear cost-effectiveness hurdles despite low budget impact. Conversely, products for more common life-threatening diseases will rarely, if ever, clear budget impact thresholds no matter how cost-effective.
- The diverse spectrum of health care stakeholders concurs on at least one goal: We all want cost-effective drugs to treat common chronic ailments that kill large numbers of people. The short-term budget impact analyses, unfortunately, negate the favorable effects of CE conclusions and, if given weight in payer and clinician decisions, could not only constrict access to current treatments, but discourage innovation of new therapeutic options.
- The $819,000,000 threshold for budget impact is based on World Health Organization (WHO) calculations. This is not based on US public policy. It introduces rationing that not only conflicts with public policy but is outside the scope of ICER's cost-effectiveness mission.
- The Steering Committee also notes that the population assessed for the rivaroxaban budget impact is overstated. ICER's calculations include all CAD and peripheral artery disease (PAD) patients, acute and chronic. The rivaroxaban indication is for chronic patients, typically > 1 year from acute coronary syndrome (ACS). Additionally, rivaroxaban would not be prescribed for patients at increased risk for bleeding. We remain concerned that budget impact calculations imply that there is an accepted societal value in rationing care, and in this context, overestimates do exacerbate our concerns. In the PCSK9 inhibitor example, just 10% of ICER's 5-year addressable population estimate were prescribed a PCSK9 inhibitor over a 3.5-year time horizon (ICER's report stated that "to not exceed this budget impact threshold, approximately 1% of eligible patients could be treated"). As noted above, a recent Circulation paper demonstrated that the undertreatment of appropriate patients led to unnecessary cardiac events. The same risk applies here with rivaroxaban and icosapent ethyl.

- Patient and caregiver time and productivity
  - As previously noted, ICER's base-case analysis took a health care sector perspective and ignored productivity losses to the patient and caregiver. Although the draft report included a scenario analysis using a modified societal perspective, we are concerned that the overall burden of CVD is not fully incorporated into ICER's draft report.

Conclusion

The Steering Committee agrees with ICER's conclusions that both rivaroxaban and icosapent ethyl are cost-effective interventions that can improve patient outcomes. We urge ICER to take a leadership role in ensuring that evidence-based analyses on cost-effectiveness are appropriately scoped to issues within their domain, and that reports adhere to scope without creeping into medical practice lanes that are, and should be, reserved for specialty societies and clinicians on the front-lines treating patients. Additionally, we strongly urge ICER to clearly state that its cost effectiveness reports should not be interpreted as supplanting, augmenting, and/or over-riding FDA determinations, guidelines from specialty societies, or the judgment of experts treating patients of varying complexity.

We ask that you consider and incorporate our comments into your final report and panel discussions, and again thank you for your consideration. We look forward to the opportunity to bring together representatives from the Steering Committee to meet with your team to further this conversation.

Sincerely,

Members of the Value & Access Steering Committee and Partners including:

National Forum for Heart Disease & Stroke Prevention (convener)
Alliance for Patient Access
American Association of Heart Failure Nurses
American Heart Association
American Pharmacists Association Foundation
American Society for Preventive Cardiology
Association of Black Cardiologists
Association of State and Territorial Health Officials
BallengeRx Consulting
FH Foundation
Global Healthy Living Foundation
Independent Health
Mended Hearts
National Association of Chronic Disease Directors
Partnership to Advance Cardiovascular Health
Partnership to Improve Patient Care
Preventive Cardiovascular Nurses Association

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