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August 20, 2019

Steven D. Pearson, MD, MSc
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RE: Comments on "Additive Therapies for Cardiovascular Disease: Effectiveness and Value" Draft Evidence Report and Draft Voting Questions

Dear Dr. Pearson,

Amarin would like to thank ICER for the opportunity to review and provide feedback on the "Additive Therapies for Cardiovascular Disease: Effectiveness and Value" Draft Evidence Report and Draft Voting Questions. Overall, we appreciate the efforts you have made in your economic analysis of icosapent ethyl. We understand both the complex nature of modeling, which often requires the use of diverse data sources and numerous assumptions, as well as the limitations of methodologies such as Markov models, which simulate and project costs and outcomes in cohorts of patients over time. For these reasons we would like to point out a few ways in which the economic analysis could potentially be strengthened in order to more thoroughly capture the cost-effectiveness and budget impact of icosapent ethyl. In our June 21, 2019 comments regarding the Model Analysis Plan (MAP) we had noted the importance of using the totality of evidence from REDUCE-IT including (1) using all five components of the prespecified primary endpoint in the Markov model base-case analysis[1] and (2) using total event data. As a result of the strong scientific evidence, these are important considerations and in addition we feel the analysis could benefit from (3) using patient-level data and a microsimulation approach, and (4) using more recent US national cost data for cardiovascular disease (CVD) events.

1. **Using all five components of the prespecified primary endpoint in the Markov model base-case analysis**

As a result of the strong scientific evidence from REDUCE-IT, it is critical and appropriate to incorporate all statistically significant and clinically meaningful endpoint data for icosapent

[1] Coronary revascularization and hospitalization for unstable angina were included as a scenario analysis only—not in the base-case. Amarin feels that scenario analyses carry less weight compared to the base-case with health care decision makers.

ethyl into the base-case Markov model to rigorously assess its economic value and budget impact. While the base-case model contains treatment-specific events for myocardial infarction (MI) and stroke (current and post-event states) as well as all-cause and CV-specific death, REDUCE-IT reported statistically significant findings for coronary revascularization and for hospitalization (≥24 hours) for unstable angina; however, these were not included as treatment-specific events in the base-case model and were only incorporated in a scenario analysis. For avoidance of doubt, these events were well defined and agreed upon as being major adverse CV events, with the US FDA prior to unblinding of the trial.

As we noted in our June 21, 2019 MAP comments, in REDUCE-IT, 16 hospitalizations for unstable angina (rate ratio [RR]: 0.69; 95% confidence interval [CI]: 0.54-0.89) and 76 coronary revascularization procedures (RR: 0.64; 95% CI: 0.56-0.74) were prevented per 1000 patients treated for 5 years (Bhatt et al. *JACC.* 2019; Bhatt et al. *NEJM.* 2019). In terms of first event analyses, hospitalizations for unstable angina achieved a hazard ratio [HR] of 0.68 (95% CI: 0.53-0.87) and coronary revascularization achieved a HR of 0.66 (95% CI: 0.58-0.76) (Bhatt et al. *NEJM.* 2019). These are clinically meaningful benefits for patients and cost offsets for payers resulting from treatment with icosapent ethyl and, as a result of the high-quality scientific evidence from REDUCE-IT, should be included in the base-case cost-effectiveness and budget impact analyses.

2. Using total event data

We still believe it is critical to utilize the totality of the evidence available on the effects of icosapent ethyl from the REDUCE-IT trial to rigorously assess its economic value and budget impact. Recurrent CV events involve real costs to patients, payers, and society which should not be understated in assessing economic value and budget impact. REDUCE-IT provides robust and complete evidence for the effects of icosapent ethyl not only in preventing a first primary composite endpoint event—CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina (Cox proportional hazards model HR: 0.75; 95% CI: 0.68-0.83) (Bhatt et al. *NEJM* 2019)—but also in reducing total CV events (negative binomial model RR: 0.70; 95% CI: 0.62-0.78) (Bhatt et al. *JACC*. 2019).

In our June 21, 2019 MAP comments, we noted that the total event analysis—the Wei-Lin-Weissfeld (WLW) model with the Li and Lagakos modification (Wei et al. *J Am Stat Assoc*. 1989; Li et al. *Stat Med*. 1997)—suggests that the first occurrence of a primary composite endpoint event was reduced with icosapent ethyl versus placebo (HR: 0.75; 95% CI: 0.68-0.83), as were the occurrences of the second event (HR: 0.68; 95% CI: 0.60-0.78) and of the third event (HR: 0.69; 95% CI: 0.59-0.82) (Bhatt et al. *JACC*. 2019). Additional total event analyses included the Andersen-Gill I model (based on an intensity model with model-based variance estimate), the Andersen-Gill II model (based on a proportional means model with cluster-robust standard errors, with the cluster set to the patient ID) (Andersen et al. *Ann Statist*. 1982; Lin et al. *J R Statist Soc*. 2000), and a joint-frailty model for nonfatal events (Rondeau et al. *Biostatistics*. 2007). Reassuringly these models provided results similar to the total event negative binomial model RR estimates: HR: 0.69; 95% CI: 0.64-0.74, HR: 0.69; 95% CI: 0.61-0.77, and HR: 0.67; 95% CI: 0.61-0.74, respectively (Bhatt et al. *JACC.* 2019). The strong agreement of an approximate 30% relative risk reduction as predicted by the modified WLW for second and third events with results for reduction of total events (first and subsequent) from multiple statistical models

(negative binomial, Andersen-Gill I and II, joint-frailty) further support the validity of the observed reductions in the total (first and subsequent) and individual (e.g., second or third occurrence) events.

In our June 21, 2019 MAP comments we noted that we realized the modified WLW individual event occurrence results may not be easily accommodated within the structure of the Markov model and, therefore, we proposed that applying the negative binomial model total event RR of 0.70 to all events would be an appropriate assumption in the base-case analyses—and as a result of the high-quality scientific evidence from REDUCE-IT, we still feel this to be the case.

3. **Using patient-level data and a microsimulation approach**

While we understand that Markov models that simulate the clinical, economic, and quality-adjusted survival outcomes for cohorts of patients over time are a valid and accepted method in economic analysis, and have been used in the health economics field for many years, we believe that patient-level data, if it were available, and a microsimulation approach, would provide important detailed information that would permit a more thorough and nuanced assessment of the value and budget impact of icosapent ethyl. CVD patients in real-world clinical practice will have many different combinations of characteristics, risk factors, comorbidities, and disease histories, and cohort-based Markov models are often unable to handle these complexities.

4. **Using more recent US national cost data**

We observe in several places within the draft report that older CVD event costs (inflated to 2019 values using the health care component of the personal consumption expenditure index) are used for the economic analysis. For example, in the study by Kazi et al. (2016), CVD event costs are derived from 2008 California Office of Statewide Health Planning and Development (OSHPD) data and in the study by O'Sullivan et al. (2011), national cost data are from the early to mid-2000s and adjusted to 2007 values. Although inflation adjustment is a valid approach in health economic analysis, it may not fully account for actual changes in costs over time and we believe that more recent CVD event cost data from a national integrated electronic medical record (EMR)/claims database, such as Optum or IBM-Watson MarketScan, could provide more accurate cost estimates.

Draft Voting Questions

For the Draft Voting Questions, we propose adding the underlined text to Questions 3, 5, 7, and 10 to be consistent with wording on page 10 of the Draft Evidence Report (i.e., "Patients are assumed to also be receiving optimal medical management including statins."):

3. For patients currently receiving <u>optimal medical management including</u> statin therapy, is the evidence adequate to demonstrate that the net health benefit of adding icosapent ethyl is superior to that provided by optimal medical management <u>including statin therapy</u> alone?

5. For patients currently receiving <u>optimal medical management including</u> statins, does treating patients with icosapent ethyl offer one or more of the following potential "other benefits or disadvantages" compared to optimal medical management <u>including statin therapy</u> alone?

7. For patients currently receiving optimal medical management including statins, are any of the following contextual considerations important in assessing the long-term value for money for icosapent ethyl compared to optimal medical management including statin therapy alone?

10. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with icosapent ethyl in addition to optimal medical management (including statins) versus optimal medical management including statin therapy alone?

Conclusion

First, all five components of the REDUCE-IT primary composite endpoint are clinically impactful and result in substantial cost implications. Due to the clinical importance of these events, the rigor under which they were collected, the consistency of benefit observed, and the relevance to both the cost-effectiveness and budget impact of icosapent ethyl, hospitalization for unstable angina and coronary revascularization should be included in the base-case. Second, using only the time-to-first-event HR in the Markov model base-case does not account for the full benefit of treatment over time and likely undervalues intervention—and overestimates budget impact—with icosapent ethyl. Accordingly, as a result of the high-quality scientific evidence from REDUCE-IT, it would be appropriate to use the total event analysis RR of 0.70 that was reported for the 5-point major adverse cardiac events (primary endpoint of REDUCE-IT) in the base-case analysis and the time-to-first-event HR of 0.75 in the sensitivity analyses. Finally, we believe that patient-level data and a microsimulation approach, and the use of more recent national US cost data (as opposed to inflation-adjusted older cost data, of which some is state-level data) for CVD events could help to strengthen the analyses.

Amarin appreciates the opportunity to provide comments on the "Additive Therapies for Cardiovascular Disease: Effectiveness and Value" Draft Evidence Report and Draft Voting Questions.

Thank you.

Sincerely,

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August 20, 2019

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Dear Dr. Pearson:

AstraZeneca has reviewed the draft ICER evidence report on Additive Therapies for Cardiovascular Disease: Effectiveness and Value. We would like to offer the following comments after reviewing the draft.

1. AstraZeneca would like to reiterate that the comparison of rivaroxaban + ASA with ticagrelor + ASA is inappropriate because of significant differences in trial designs, populations studied, and indications. We appreciate ICER having a similar view as put forward on page 39 and 40 of the draft evidence report.

2. The report fails to include important characteristics that speak to the uniqueness of ticagrelor, from both the label and guidelines perspective.
    a. The draft evidence report cites the 2016 ACC/AHA guideline on page 15 but omits that ticagrelor is preferred over clopidogrel in both ST-elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTE-ACS).[1]
        i. The guideline includes a Class IIa level of evidence B-R recommendation that in patients with acute coronary syndrome (ACS [NSTE-ACS or STEMI]) treated with DAPT after coronary stent implantation and in patients with NSTE-ACS treated with medical therapy alone (without revascularization), **it is reasonable to use ticagrelor in preference to clopidogrel** for maintenance $P2Y_{12}$ inhibitor therapy.
    b. The superiority of ticagrelor over clopidogrel has also been clearly stated in its indication for ACS.[2]
        i. BRILINTA is indicated to reduce the rate of cardiovascular death, myocardial infarction (MI), and stroke in patients with ACS or a history of MI. **For at least the first 12 months following ACS, it is superior to clopidogrel.**
    c. Clopidogrel is no longer indicated for patients who are treated with PCI during a STEMI, while ticagrelor is indicated in patients with ACS regardless of treatment strategy.[3,4]

3. Albeit ICER acknowledged the insufficient evidence and lack of head to head trials comparing rivaroxaban + ASA, ticagrelor + ASA, and clopidogrel + ASA, a Network Meta-analysis (NMA) was performed. Though we respect the rationale for doing such an analysis, we do have concerns with the results stated in Table 3.8 on page 29 of the draft evidence report. The CHARISMA study is used as a comparator for this analysis. Please note that the population in CHARISMA is more similar to the population in COMPASS than PEGASUS, and the patients with a prior MI in CHARISMA were a subset of the overall CHARISMA

population.[5,6,7] Furthermore, CHARISMA failed to meet its primary endpoint; as such any subgroup analysis from this study should be considered hypothesis generating at best.[7] The numbers contributed by CHARISMA and COMPASS in the NMA are quite small, relative to the numbers contributed from PEGASUS. It is unclear whether such trial characteristics were considered in the NMA.

There are no randomized, head to head, large scale outcomes trials comparing clopidogrel + ASA to ticagrelor + ASA in prior MI. The only data that does exist comparing the agents is in ACS and showed superiority of ticagrelor + ASA over clopidogrel + ASA. Hence, we request that ICER remove the 1.00 (0.75 to 1.32) in Table 3.8.

4. The draft evidence report QALY analysis focuses on rivaroxaban + ASA compared to clopidogrel + ASA. The terminology used through most of the document simply states "DAPT." We request that ICER use more specific terminology and mention the actual analysis conducted which is rivaroxaban + ASA compared to "DAPT with clopidogrel."

5. A major concern we have is the interpretation of such a document and the comparative analysis performed when viewed by clinicians treating patients. Currently DAPT is recommended for at least 12 months (with an assessment at six months for residual bleeding and ischemic risk) in all patients with an ACS.[1] Hence, patients with a prior MI will have been on DAPT. This analysis could be interpreted as a tacit approval to switch between treatment regimens involving either another $P2Y_{12}$ inhibitor or an anti-thrombin. It is important to note that such switching between agents has never been formally studied from an "outcomes" perspective and CHARISMA and COMPASS analyzed initiation of therapy and not switching.[5,7,8] If anything, such switching should be discouraged as it can expose patients to undue ischemic and bleeding risks. Hence, we recommend that a clear statement be made in the document that any analyses contained in the report regarding patients with a prior MI should not be used to guide clinical management of such patients.

Yours truly,

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Date: August 20, 2019
RE: ICER Additive Cardiovascular Disease Therapies Draft Evidence Report – Response to Request for Public Comment

The following information is provided in response to request for public comment and is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the full Prescribing Information for each product, including the following sections: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, AND ADVERSE REACTIONS.

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EXECUTIVE SUMMARY

- XARELTO® (rivaroxaban) is an important and valuable treatment option for people with chronic coronary artery disease (CAD) and/or peripheral artery disease (PAD) who are at risk of devastating and potentially irreversible cardiovascular events, including strokes, heart attacks and death. We expected the ICER analysis to reinforce the value of XARELTO® in patients with chronic CAD and/or PAD, and find XARELTO® highly cost effective in this setting. However, we do not endorse the use of cost-per-QALY or cost-per-life-year-gained analysis as the sole or primary basis of decision making.
- Presentation of XARELTO® and icosapent ethyl results side by side as presented in the draft evidence report is misleading and may lead to incorrect clinical and economic comparison of XARELTO® to icosapent ethyl as it suggests they have interchangeable benefits. As such, Janssen recommends ICER entirely separate the presentation of these data in the text and tables throughout the report.
- Dual antiplatelet therapy (DAPT) is not an appropriate comparator given the differences in study designs, study populations, indications, efficacy and safety endpoints. Furthermore, it is not appropriate to compare results from a post hoc subgroup analysis of a clinical trial (e.g., CHARISMA) that did not meet its' primary endpoint, when there is a proven clinical benefit with a highly powered contemporary clinical study that met its primary endpoint (e.g., COMPASS).
- The prevalence estimates used by ICER in the budget impact analysis are grossly overestimated. They are not representative of the patients included in the COMPASS trial and are not indicative of the patients that would be eligible to be treated as per the FDA-approved XARELTO® indication, which includes only chronic CAD or PAD. ISPOR's principles of good practice for budget impact analysis recommends use of eligible patient population for indication (Sullivan SD 2014).
- ICER's budget impact analysis reporting that only 6% of the eligible patients could be treated per year with XARELTO® is misleading. We question the methods on how ICER conducts budget impact assessment that appears inapplicable for cardiovascular disease (CVD) patient population.

PRESENTATION OF XARELTO AND ICOSAPENT ETHYL DATA

GLOBAL COMMENT:

JANSSEN does not agree with presentation of XARELTO® and icosapent ethyl results side by side throughout the text and outcomes tables within the draft evidence report as this is misleading and may lead to incorrect clinical and economic comparison of XARELTO® to icosapent ethyl as it suggests they have interchangeable benefits.

- COMPASS and REDUCE-IT had significant differences in study design, study populations and outcomes measures and should not be compared directly or indirectly (Eikelboom 2017; Bhatt 2019).

- XARELTO® and icosapent ethyl are two distinct molecules that address different pathways in the overall management of stable CVD.
    - Icosapent ethyl is a purified ethyl ester of the omega-3 fatty acid known as eicosapentaenoic acid (EPA), which was initially approved in 2012 as an adjunct to diet to treat severe hypertriglyceridemia (triglyceride levels ≥500 mg/dL).
    - XARELTO® addresses the thrombotic component of stable CVD, and has been proven to reduce the risk of major cardiovascular (CV) events [CV death, myocardial infarction (MI), and stroke] in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD) when used in combination with aspirin.
- Additionally, using the same baseline estimates of CAD patient population for both XARELTO® and icosapent ethyl gives the false impression that they are indicated in the same patient population.
- Of note, the COMPASS trial, which focused on patients with stable atherosclerotic CVD did not specifically require or record statin use or lipid levels (Eikelboom 2017). In contrast, all patients in REDUCE-IT were required to be receiving statin therapy, to have established CVD or diabetes plus other risk factors, and to have controlled LDL levels on statin therapy (Bhatt 2019).

PREVALENCE ESTIMATES USED IN THE BUDGET IMPACT ANALYSIS

Page #9: Section # 1.1:

Please note XARELTO® is indicated for use in patients with "chronic" CAD or PAD. As such, please revise intervention and other subsections to include "chronic" when referring to XARELTO® in patients with CAD or PAD.

- XARELTO® (rivaroxaban) a selective factor Xa inhibitor anticoagulant, in combination with aspirin, is indicated to reduce the risk of major cardiovascular (CV) events [CV death, myocardial infarction (MI), and stroke] in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD) (XARELTO PI).

Page #68, Section #7.2:

- The prevalence estimates used by ICER in the budget impact analysis are grossly overestimated. ICER's draft evidence report states: "We assumed that patients matching those in the respective trials would be eligible for rivaroxaban". However, the eligible prevalent patient population for XARELTO®, 6.7% of the United States (US) population (age ≥20) considered by ICER is not representative of the patients included in the COMPASS trial and is not indicative of the patients that would be eligible to be treated as per the FDA-approved XARELTO® indication.
    - ICER should follow ISPOR's principles of good practice for budget impact analysis by estimating eligible population of approved indications for the new technology (Sullivan 2014). The exclusion criteria used in the COMPASS trial was not considered.
- The FDA approved indication for XARELTO® includes only patients with 'chronic' CAD or PAD. ICER's Potential Budget Impact Analysis includes both acute and chronic CAD patients in the US. JANSSEN recommends use of appropriate eligible patient population based on the FDA approved indication for XARELTO®.
- Additionally, using same baseline estimates of CAD patient population for both XARELTO® and icosapent ethyl gives the false impression that they are indicated in the same patient population.

COMPARISON TO DAPT

Page #11: Section # 1.2:

Janssen does not support dual antiplatelet therapy (DAPT) as an appropriate comparator given the differences in study designs, study populations, indications, efficacy and safety endpoints. These differences are further described in greater detail in prior submissions to ICER.

- DAPT is not an appropriate comparator to XARELTO®, as it is not a recommended standard of care for chronic CV disease, and furthermore, it is not appropriate to compare results from a post hoc subgroup analyses of a clinical trial (e.g., CHARISMA) that did not meet its' primary endpoint, when there is a proven clinical benefit with a highly powered contemporary clinical study that met its' primary endpoint (e.g., COMPASS).

Page #29: Section # 3.3

- In the network meta-analysis (NMA), ICER evaluated the impact of XARELTO® plus aspirin (ASA) vs. DAPT in the subgroup of patients with a recent myocardial infarction [MI (i.e., MI within 2 years prior to randomization]. It is important to note however, that patients with <2 years of history of MI represent only 13% of the COMPASS trial population (Connolly 2018).
- The COMPASS trial was not powered to detect a difference among patients with <2 years of history of MI. Using hazard ratio estimates derived from sub-populations not powered to detect such differences and then utilizing these underpowered estimates to make indirect comparison with DAPT therapies is inaccurate and may lead to misleading clinical conclusions.

Page #53, #60: Section # 4.3

- Using these inaccurate estimates generated from the NMA in cost-effectiveness analysis further leads to inaccurate economic results.
- In addition, the approach of equating the annualized major bleeding rates in this analysis can lead to inaccurate conclusions of cost effectiveness between XARELTO® and DAPT.
- Due to considerable limitations of the NMA of XARELTO® + ASA vs. DAPT analysis we encourage ICER to exclude these results from the report.

STROKE OUTCOMES

Page #49: Section #4.2:

The draft evidence report does not capture the indirect societal costs and factors important to patients associated with debilitating outcomes including strokes, amputations, and heart attacks.

- Strokes for example, are very diverse in nature specifically in degree of irreversible disability. The post-hoc analysis of the COMPASS trial showed that XARELTO® plus aspirin not only reduced the number of strokes but also the occurrence of fatal and disabling strokes (modified Rankin Scale, 3-6) (Sharma 2019). Health utilities vary significantly for different stroke severities (Ali 2017) and should be captured accordingly. Similarly, the healthcare costs for managing strokes are different based on the debilitating nature of the stroke. Costs for managing highly debilitating strokes are not similar to managing strokes which result in mild disability.

Page #53: Section #4.2:

- Furthermore, indirect costs assumptions for absenteeism of 13.6 hr/month is far from adequate assumption of indirect costs caused by stroke. Stroke patients with severity of Modified Rankin Score, mRS≥3 would very likely go on permanent disability and claim Social Security Disability after Stroke (Medford-Davis 2016, Disability Benefits).

LONG TERM COST EFFECTIVENESS

Page #52, Table 4.11:

- ICER assumes that the price of XARELTO® will remain steady with 3% of price increase per year until all patients in the model have reached mortality, which is an inaccurate assumption.
- XARELTO® has been on the US market for 8 years since it first received US FDA approval in 2011. After loss of patent exclusivity, generic price of small molecules is generally significantly lower than the branded drug (Vondeling GT 2018, Kelton C, 2014). As such it may be reasonable to expect that the cost effectiveness model would use a generic price of XARELTO® at some pre-defined point over the lifetime of the model. The inclusion of generic price for XARELTO® would significantly impact cost effectiveness results in the model.

POTENTIAL BUDGET IMPACT ANALYSIS

Page #68; Section #7:

- ICER's budget impact analysis concludes that US could only afford to treat 6% of the eligible patients in a given year with XARELTO® without crossing a threshold aligned with overall growth of

the US economy. The short-term affordability framework based on drug spending and gross domestic product (GDP) in the US seems unrealistic and inapplicable for CVD therapies.

- We wanted to understand how many CAD patients could be treated with aspirin under the defined threshold of $819MM using ICER's budget impact methodology. We considered the eligible population for aspirin proposed by this report (i.e. 16,908,000 patients over 5 years) and annual price for aspirin of $18.
- The proportion of patients that could be treated with aspirin without crossing the budget impact threshold was found to be around 50%-70%.
- Aspirin is known to be one of the most readily and cheaply available treatments for primary and secondary prophylaxis in CVD population. As per ICER's budget impact framework, US cannot afford to treat all 16.9 million patients with aspirin.

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AIMED ALLIANCE

August 19, 2019

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Boston, MA 02109

Dear Dr. Pearson:

Aimed Alliance is a 501(c)(3) non-profit health policy organization that seeks to protect and enhance the rights of health care consumers and providers. Aimed Alliance respectfully submits the following comment in response to the "Additive Therapies for Cardiovascular Disease: Effectiveness and Value Draft Evidence Report" ("Cardiovascular Draft Report") published by the Institute of Clinical and Economic Review (ICER) on July 30, 2019.

Cardiovascular disease ("CVD") is the leading cause of death in both men and women in the United States.[1] CVD refers to a number of conditions that affect the heart and blood vessels, including heart attack, stroke, heart failure, arrythmia, and heart valve problems.[2] Approximately 850,000 Americans die from CVD each year.[3] Moreover, about 735,000 Americans suffer from a heart attack each year. For roughly 525,000 individuals, this will be their first heart attack, while about 210,000 will have previously experienced one.[4] Depending on the particular condition, CVD is typically treated in one of three ways: lifestyle changes, medications, and medical procedures or surgery, such as coronary revascularization.[5] CVD also creates a significant financial burden on patients, their families, and the United States health system as a whole. Direct and indirect costs of CVD are estimated to be $330 billion each year.[6]

Because of the enormous prevalence of CVD in the United States and the numerous forms in which CVD can manifest, access to a variety of treatment and management options is critical.[7] Aimed Alliance appreciates that ICER has deemed icosapent ethyl and rivaroxaban cost effective, and we respectfully request that you consider the following information when developing your value-based price benchmarks.

I. Inappropriate to Compare Icosapent Ethyl and Rivaroxaban

Aimed Alliance cautions against comparing the effectiveness and value of icosapent ethyl and rivaroxaban because icosapent ethyl and rivaroxaban have different methods of action within the human body and are intended for different uses. Icosapent ethyl is indicated for use in adults to "reduce triglyceride levels in patients with severe hypertriglyceridemia"[8] while rivaroxaban is indicated for "reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial

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[1] https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_disease.htm
[2] https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_disease.htm, https://www.heart.org/en/health-topics/consumer-healthcare/what-is-cardiovascular-disease
[3] https://www.ncbi.nlm.nih.gov/pubmed/30700139
[4] https://www.cdc.gov/heartdisease/facts.htm
[5] https://www.mayoclinic.org/diseases-conditions/heart-disease/diagnosis-treatment/drc-20353124
[6] https://www.mdmag.com/medical-news/heart-break-preventive-aspirin-use-physical-activity-on-the-decline
[7] https://www.heart.org/en/get-involved/advocate/federal-priorities/access-to-care
[8] https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202057s009lbl.pdf

defibrillation,"[9] and for the treatment, prevention, and reduction of the recurrent risk of deep vein thrombosis and pulmonary embolism.[10] Therefore, we caution ICER against conducting a comparative effectiveness analysis of these two medications because they are not substitutes for each other.

II. ICER Must Consider Patients' Perspective

While ICER acknowledges the patient perspective, it should incorporate the direct and indirect costs to patients in its calculations. Patients with CVD who do not receive treatment have higher incidences of productivity loss, including days of work lost among employed individuals, home productivity lost, and work loss among individuals too sick to work.[11] Moreover, families of individuals who die prematurely incur the value of lost earnings.[12] Factors such as these should be considered in ICER's analysis.

III. Exclusion of Valuable Data

When determining the effectiveness of icosapent ethyl, the REDUCE-IT study considered five primary endpoints: cardiovascular-related death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization due to unstable angina. Yet, while ICER considered all five endpoints in its sensitivity testing, it excluded coronary revascularization and hospitalization due to unstable angina in its base case. Coronary revascularization, such as coronary artery bypass surgery (CABG), and hospitalization are both costly adverse events that should be considered in a cost-effectiveness analysis. The estimated costs of initial hospitalization for CABG has been estimated to be $34,467.[13] Moreover, patients who have had a secondary CVD-related hospitalization have been found to have annual costs associated with their treatment that are 4.5 times higher than patients who were not hospitalized.[14] Moreover, when conducting a cost-effectiveness analysis based on clinical trials, it is important to utilize all primary endpoints in those trials rather than selecting certain endpoints over others.

Additionally, ICER only considered the effect of icosapent ethyl on the time to first events rather than total ischemic events (first plus subsequent events). Yet, all adverse events directly and indirectly impact patients' lives. Subsequent events can be costly, and therefore, a proper cost-effectiveness analysis should take those expenses into account.

IV. Use of QALYs is Inappropriate

Aimed Alliance reiterates its longstanding recommendation against relying on quality-adjusted life year (QALY) measures to evaluate any treatment, including preventive CVD treatments. The use of QALY measures to evaluate cardiovascular disease raises significant ethical concerns. QALY measures put a price tag on the value of human life that merely reflects the

[9] https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202057s009lbl.pdf
[10] https://www.xareltohcp.com/dvt-pe
[11] https://healthmetrics.heart.org/wp-content/uploads/2017/10/Cardiovascular-Disease-A-Costly-Burden.pdf
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[13] http://icer-review.org/wp-content/uploads/2016/01/Costs-PCI-CABG-DM-CAD-March-2013.pdf
[14] https://www.ajmc.com/journals/issue/2010/2010-03-vol16-n03/ajmc_10marnicholswebx_e86to93

individual's diagnosis and deems those with chronic, debilitating, and rare conditions as being worth less than those with common conditions. They treat individuals' lives and health as a commodity and ignore patients' and practitioners' individualized concept of the value of treatment.

Individuals with CVD may face challenges in obtaining consistent treatment due to barriers to health insurance coverage.[15] Health plans may impose high copays, prior authorization, or step therapy limits on coverage that result in a significant financial burden on patients.[16] As a result, patients ration their medications, and this lack of adherence to a treatment plan can result in higher rates of cardiovascular-related emergency room visits as well as preventable deaths.[17] The American Heart Association estimates that medication nonadherence results in approximately 125,000 preventable deaths each year.[18] A recent study found that 20.6 million people with cardiovascular disease and its risk factors still lacked health insurance.[19] QALYs are often used to justify coverage limitations that prevent individuals from obtaining treatments that are most appropriate for their individualized needs. For these reasons, we recommend against using QALYs.

V. A Value Assessment is Premature

While clinical trials have provided evidence of the safety, effectiveness, and value of icosapent ethyl for the treatment of hypertriglyceridemia, these treatments are still in their infancy. While icosapent ethyl was approved by the FDA in July 2012, the FDA is currently considering a new indication for reducing cardiovascular risk. Pending approval, valuable data will fully emerge in clinical practice. However, if icosapent ethyl is deemed inadequately cost-effective now, then the likelihood of third-party payers covering the treatment for new indications without imposing significant benefit utilization management policies increases, creating barriers to access for individuals who need them. Without market uptake, data cannot be collected and analyzed. Therefore, we recommend that ICER refrain from making a determination on the value of this treatment until mature data emerges.

VI. Conclusion

Thank you for the opportunity to comment on the Cardiovascular Draft Report. We offer our assistance in working closely with ICER to address our shared goals of improving access to high quality health care at a price that accurately reflects public and personal benefits.

Sincerely,

John Wylam
Staff Attorney

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[15] https://www.heart.org/-/media/files/about-us/policy-research/fact-sheets/access-to-care/fact-sheet-breaking-down-the-barriers-the-uninsured-with-heart-disease-and-stroke.pdf?la=en&hash=A789BC3E0158657CA4E47490EEF0528D6ED67CBB

[16] http://1yh21u3cjptv3xjder1dco9mx5s.wpengine.netdna-cdn.com/wp-content/uploads/2016/11/CWG-WhitePaper-Nov2016_FINAL.pdf; https://www.ahajournals.org/doi/10.1161/CIR.0000000000000652

[17] https://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_460769.pdf

[18] https://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_460769.pdf

[19] https://link.springer.com/article/10.1007/s11606-019-05108-1

July 25, 2019

Steven D. Pearson, MD, MSc
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RE: Draft Evidence Report on Additive Cardiovascular Disease Therapies

Dear Dr. Pearson:

Thank you for the opportunity to submit comments in response to the Institute for Clinical and Economic Review's (ICER) draft evidence report on additive therapies for cardiovascular disease. The following comment, hereby submitted by Medical Research Collaborative, LLC, contains a modified portion of the analysis that comprises our recently submitted 83-page FDA Citizen Petition,[1] itself based upon available information on past clinical trials testing the compound, icospaent ethyl, aka Vascepa®, including the REDUCE-IT trial. Our analysis demonstrates that the REDUCE-IT trial results are likely confounded by the use of the mineral oil placebo, which may have markedly attenuated the efficacy of multiple concomitant cardiac medications taken by subjects in the trial's placebo group.

In its draft report, ICER has taken the view that, "Although we are uncertain whether the use of mineral oil may have caused some harm to the placebo group, we do not believe that this theory can account for the entire benefit observed in the REDUCE-IT trial." However, ICER gives no additional input, and chooses to then use the entire recorded benefit from the trial in their modeling, despite Dr. Bhatt's statement that the actual primary MACE composite RRR could be closer to 20% (and thus, all other endpoints also less impactful). Our analysis suggests that accepting the premise that the stated percentage reductions from the trial results are the most reliable datapoints to base modeling on will result in misleading cost-effectiveness analyses.

Please consider our comment herein and especially our greater analysis contained in the Citizen Petition cited above as you finalize your report that will be relied upon by payors[2] to the benefit or detriment of all present and future U.S. citizens (and marine ecosystems), and consider delaying the portion involving Vascepa® until FDA arrives at their own conclusions, having the exclusive benefit of being able to view the entire dataset.

Background

The REDUCE-IT trial results were presented at the AHA Scientific Sessions on November 10th, 2018, along with a paper released in the NEJM on the trial, sponsored by Amarin Corp. Data were glowingly positive on the primary and nearly all secondary endpoints. The relative risk reduction (RRR) of ASCVD events was 25% for treatment group, heralding the therapy (icosapent ethyl, a highly purified fish oil composed of >95% ethyl ester eicosapentaenoic acid (EPA-E), brand name Vascepa®) as a potential landmark treatment for high risk primary prevention and secondary cardiovascular disease patients with persistently elevated triglycerides (135 mg/dL - 499 mg/dL).

However, in the Discussion section of the NEJM paper,[3] there was a mention expressing the potential that light paraffin oil (aka "mineral oil," hereafter abbreviated "MO") placebo may have adversely impacted statin absorption in some unknown number of subjects:

> "Our trial has certain limitations… **[I]f mineral oil in the placebo affected statin absorption in some patients, this might have contributed to differences in outcomes between the groups.** However, the relatively small differences in LDL cholesterol levels between the groups would not be likely to explain the 25% lower risk observed with icosapent ethyl…"

This is a perplexing statement, because it casts the results into ambiguity. The question arises, "To what extent is the stated 25% RRR overblown?" The authors (who it must be admitted may be biased[4]) attempt to answer this with three points, the first being, *"The relatively small differences in LDL-C levels between groups would not be likely to explain the 25% lower risk observed with icosapent ethyl."* Elsewhere the Global Principal Investigator, Dr. Bhatt, provided color to this statement, suggesting the increase in LDL-C in MO placebo group infers at most a lowering of the MACE composite RRR from 25% to 20%.[5] But is this speculation sanguine?

Effect of Between-Group Differences in Biomarkers on ASCVD Event Risk

The 2013 ACC/AHA guidelines[6] introduced a paradigm shift in our perspective on LDL-C targets in favor of matching intensity of statin therapy with a patient's risk category over achieving LDL-C goals, due to a lack of RCTs testing ASCVD risk reduction based on numeric level of LDL-C achieved (only meta-analyses provide these extrapolated data). Instead, all statin trials compared a set intensity of therapy against placebo or another, usually lower intensity, statin. These data suggest that two patients of similar risk strata will achieve similar risk reductions with similar percent reductions in LDL-C as a result of statin therapy, more or less regardless of baseline values. The updated guidelines (Nov 2018) reiterate the same, summarizing current thinking below:

> "In large RCTs of cholesterol-lowering therapy, LDL-C lowering has been consistently shown to reduce the risk of ASCVD… In clinical practice, however, absolute responses in LDL-C to statin therapy depend on baseline LDL-C concentrations**. A given dose of statins produces a similar percentage reduction in LDL-C levels across a broad range of baseline LDL-C levels. For this reason, a more reliable indicator of statin efficacy is percentage reduction**. In the present document, the percentage reduction is used in follow-up monitoring of patients to estimate the efficacy of statin therapy. As a rough guide, **a lowering of LDL-C levels of 1% gives an approximate 1% reduction in the risk of ASCVD**…"

Thus, if one patient has a 5-year ASCVD risk of 20% and a baseline LDL-C of 240 mg/dL, and experiences a 3 mmol/L reduction in LDL-C as a result of statin therapy, they will obtain a similar risk reduction as another patient with a 5-year risk of 20% and a baseline LDL-C of 160 mg/dL that experiences a 2 mmol/L reduction in LDL-C—because they both achieved the same percentage lowering (~48%). The difference in absolute point reduction in LDL-C between the two patients is less relevant. Percentage reductions in LDL-C across various statin regimens and dosages are also predictive, regardless of pre-statin levels.[7]

An analysis of various dose-effects of atorvastatin showed that a 9.8-percentage point difference in LDL-C reduction between subjects represented an approximate 4-fold difference in statin dose.[8]

> "Atorvastatin 2.5 to 80 mg/d causes a linear dose-response reduction in percent change from control of blood total cholesterol and LDL-cholesterol. Manufacturer-recommended atorvastatin doses of 10 to 80 mg/d resulted in 37.1% to 51.7% decreases in LDL-cholesterol**.** From the slope of the lines, it can be seen that **for every two-fold increase**, a 3.6% and **4.9% decrease** in blood total cholesterol and **LDL-cholesterol**, respectively, was noted."

Other atherogenic markers likewise show predictable changes between statin dosages. For example, rosuvastatin has been shown to reduce non-HDL-C by 42.0% at the 10 mg dose and 50.9% at the 40 mg dose. Therefore, an approximate 9-percentage point greater reduction resulted from 4-fold the statin dose. It also reduced apoB by 36.7% to 45.3% between the 10 mg and 40 mg dose, demonstrating an 8.6-percentage point

greater reduction from 4-fold the dose. CRP levels are also lowered in a dose-response manner from statin therapy.[9] Thus, the increase in LDL-C in placebo group in REDUCE-IT, concurrent with highly significant increases in all other atherogenic markers (representative of statin malabsorption), could infer *a multi-fold reduction* in the effect of the administered statin dose.

Extrapolating the Potential Attenuation of Statins in the REDUCE-IT Trial

In REDUCE-IT, the percentage increase in LDL-C from baseline in placebo group at 1 year, 2 years, and 3 years was 10.9%, 11.4% and 10.5%, respectively. These same timepoints saw marginal LDL-C decreases in Vascepa® group of -1.2%, -0.2%, -1.2%, respectively. Not only LDL-C, but apoB, non-HDL-C, and CRP increased significantly from baseline in placebo group (+7.8%, +9.8%, +32.3%, respectively at year 2, vs -2.5%, -3.1%, -13.9% for Vascepa® group). These percentage differences in biomarkers between groups in REDUCE-IT are uncannily similar to what would be expected between groups given different intensity statins. And by the 5th and 6th years of the trial, these elevated levels began to lower in the placebo group, possibly from the uptick in dropouts ceasing dosing with MO.

In the Treating to New Targets (TNT) trial, subjects with stable CHD were randomized to either 10 mg or 80 mg atorvastatin groups. All subjects began on 10 mg/d and experienced a 35% reduction in LDL-C from 152 mg/dL to 98 mg/dL. Half of the subjects were then randomized to 80 mg/d, and experienced a further reduction in LDL-C to 77 mg/dL, representing a total reduction from baseline of ~49%. Thus, the absolute difference in LDL-C reduction between groups was ~14%.[10] In the STELLAR trial, an approximate 14-percentage point greater reduction in LDL-C also resulted from the 80 mg dose vs the 10 mg dose (36.8% vs 51.1% with atorvastatin). In both instances, the moderate discrepancy in LDL-C reduction corresponded with an *8-fold difference* in statin dose.

However, in order to determine what degree of statin malabsorption the ~11% increase in LDL-C in placebo group might represent, we would need to know the REDUCE-IT subjects' pre-statin LDL-C levels. Fortunately, this can be calculated with a fair degree of accuracy, given the reliable percent-decreases observed across doses in studies involving statins.

With a baseline LDL-C level in the supplement to the REDUCE-IT trial of 86.7 mg/dL (Hopkins) for placebo group, and all subjects on background statin therapy, our calculation using data on the statin intensity level breakdown in REDUCE-IT allowed us to derive a pre-statin LDL-C value of ~146 mg/dL (please see pgs. 7 – 8 of our Citizen Petition[11] on how we derive this calculation). Thus, a return and stabilization to around 96 mg/dL in this group represents a reduction of 34% from pre-statin levels, and an absolute difference in LDL-C of ~7% between arms. This could indicate a *nearly 4-fold reduction* in the administered statin dose.

The Role of CRP in Evaluating ASCVD Event Risk in REDUCE-IT

Going beyond extrapolations based on differences in atherogenic markers, the sharp increase in hs-CRP levels in MO placebo group in REDUCE-IT, which was observed early on and was maintained until the end of the trial, provides further evidence of the heightened risk of this group.

Data have routinely demonstrated an increased prevalence of ASCVD events amongst patients with elevated levels of CRP, particularly in those with hs-CRP levels above 2.0 mg/L. This is independent of and additive to extrapolations based on LDL-C, as was thoroughly demonstrated in an analysis of the PROVE-IT and IMPROVE-IT studies.[12]

An analysis of the EXAMINE trial showed those with levels > 3.0 mg/L had a markedly increased risk of an ASCVD event, irrespective of other risk factors.[13] This was also confirmed in analyses of the A to Z[14] and FOURIER[15] trials. The JUPITER trial,[16] which pre-selected subjects with elevated hs-CRP, showed a 44% RRR

from rosuvastatin therapy, which is markedly higher than other statin trials in demographics with lower CRP levels showed.[17] And, recently, a significant reduction in ASCVD event risk as a result of reducing CRP directly, without impacting LDL-C or other lipid/ lipoprotein levels, was demonstrated in the CANTOS trial, particularly in those that achieved hs-CRP < 2.0 mg/L.[18]

In REDUCE-IT, median levels of hs-CRP were 2.2 mg/L for icosapent ethyl (IPE) group and 2.1 mg/L for MO placebo group at baseline. At year 2, those levels were 1.8 mg/L and 2.8 mg/L, with a 13.9% reduction (p=0.04) and 32.3% increase (p<0.001) noted, respectively.

Much of the reduction in hs-CRP levels from baseline in IPE group may be explainable as regression to the mean, as one of the potential additional risk factors listed in the inclusion criteria for primary prevention subjects was a hs-CRP level > 3.0 mg/L. The trial thus preferentially selected for those with acutely elevated as well as chronically elevated CRP levels in its primary prevention segment (~30% of all subjects). We might therefore expect values in both groups to lower somewhat as inflammatory markers returned to normal in those with a temporary elevation.

A similar regression to the mean in hs-CRP levels was also seen in the JUPITER and CANTOS trials, wherein all subjects were required to have elevated levels for study entry (hs-CRP > 2.0 mg/L). Interestingly, in both of these trials, a baseline value of about 4.2 mg/L was noted across arms, which subsequently regressed to ~3.5 mg/L soon after randomization. This level was then maintained for years until the end of both trials.

Also, in two separate studies testing 4 g/d IPE in subjects for 12 weeks after an extensive stabilization period (largely controlling for regressions to the mean), hs-CRP levels had only decreased insignificantly by 3 – 4% from baseline in the IPE groups of either trial.[19] Furthermore, no significant effect on CRP has been noted from almost every clinical trial testing EPA or EPA+DHA formulations of various dosages, durations, and patient populations to date.[20]

These observations increase the likelihood that the 13.9% significant reduction in hs-CRP levels from baseline in IPE arm observed in REDUCE-IT was largely the result of a regression to the mean rather than a treatment effect of EPA, and make the sharp increase in placebo group that occurred despite this tendency, noteworthy.

Log-transformed hs-CRP Data

A line in the supplement to the NEJM paper on REDUCE-IT cites the result of an analysis of log-transformed hs-CRP data, showing a highly significant 21.8% reduction in IPE group, and no change from baseline in the placebo group. The sponsor's website provides an explanation for the analysis, stating that "individual outlier results can affect a mean or median population measurement in a way that can convey a misleadingly skewed result for the population studied."[21]

However, with a trial as large as REDUCE-IT, and with nine separate fasting lipid panels performed on average per subject to ascertain levels,[22] log-transforming these biomarker data is unnecessary,[23] and an analysis based on such could be misleading. The Central Limit Theorem states that the means of large samples will closely follow a normal distribution, whatever the distribution of the observations themselves.[24] Generally, this is considered true in samples of even modest size where skewness and kurtosis are low, but certainly in samples of over 500 subjects where skewness and kurtosis are high.[25] With over 4,000 subjects per arm in REDUCE-IT, and with each and every one contributing to overall biomarker statistics, untransformed hs-CRP data will follow a normal distribution (mean and median approximately equal), regardless of the presence of outliers.

Further, log-transformation has been shown at times to have significant drawbacks, such as causing right-skewed data to become left-skewed (and even increase skewness), and increasing instead of reducing the variability of data, whether or not there are outliers.[26]

Therefore, with regards to the robustly sized REDUCE-IT trial, an analysis based on classical statistical methods is most appropriate, such as using a t-test.[27]

To What Extent Do the Increased Levels of Atherogenic and Inflammatory Markers in the REDUCE-IT Placebo Group Confound the Trial's Results?

In the TNT trial, the 80 mg/d atorvastatin arm achieved a 30.2-percentage point greater reduction in hs-CRP compared with the 10 mg/d arm, along with a 14-percentage point greater reduction in LDL-C. This translated to a 22% RRR in MACE. In the REAL-CAD trial, the 4 mg/d pitavastatin arm achieved a 20-percentage point greater reduction in hs-CRP than the 1 mg/d arm, along with a 15-percentage point greater reduction in LDL-C. This translated to a 19% RRR in MACE. And in CANTOS, a 37% reduction in hs-CRP compared to placebo—with no difference in LDL-C, apoB, or non-HDL-C between groups—yielded a 15% RRR in MACE.

It is reasonable to deduce that the robust CRP reduction in the TNT trial contributed to the 22% RRR seen there, largely accounting for the 1.6% relative reduction in MACE for every 1% reduction in LDL-C noted in the trial. In the REAL-CAD trial, the 4 mg/d group experienced a less pronounced reduction in hs-CRP levels versus the 1 mg/d arm than the between-group differences in hs-CRP in the TNT trial (although still robust), and demonstrated a 1.3% RRR for every 1% decrease in LDL-C. Both examples are a good deal higher than the 1%/1% enumerated in ACC/AHA guidelines. In addition, CANTOS proved that a marked and sustained reduction in CRP levels favorably impacts ASCVD event risk.

One cannot rule out the potential for the ~7% difference in absolute LDL-C reduction between groups in REDUCE-IT to infer a more than 7-percentage point correction to the stated 25% RRR, considering the sharp increase in hs-CRP (+32.3%) in placebo group, which was observed soon after randomization and was maintained for the length of the trial—and despite what appears to be a contrariwise regression to the mean in hs-CRP levels in IPE arm (that should have equally impacted both groups). Using the 1.6%/1% ratio seen in TNT, that would equate to an 11.2-percentage point removal from the 25% RRR in MACE, resulting in a *13.8%* corrected RRR.

However, it could be even lower, as we have extrapolated the above detraction from the reported 25% RRR based on changes in values in the MO placebo group, which comprised over 4,000 subjects—yet, the 25% RRR calculation in actuality only involved some 900 of these 4,000 subjects, or a little less than 1/4th. Just what were the changes in LDL-C, non-HDL-C, LDL-P, apoB, TG, hs-CRP, etc. in these ~900 placebo group subjects that had an event? Were these levels more elevated in those subjects that had an event vs those that did not? What if LDL-C increased over 20% and hs-CRP over 40% in such subjects, a disproportionate percentage of whom were on high-intensity statins (thus, higher baseline risk)? Only the sponsor and, now, the FDA, know.

While this discussion on statin malabsorption by itself is troubling, it appears another potential confounder has just presented itself: if MO quite possibly inhibited statin absorption in placebo group (observable by highly significant increases in LDL-C, apoB, non-HDL-C and CRP from baseline), does that not increase the likelihood of malabsorption of other cardiac medications, such as antithrombotics and antihypertensives? We think the evidence of this also is compelling, and cover it in detail on pgs. 19 – 23 of our Citizen Petition.[28]

Respectfully submitted,

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President and CEO
Medical Research Collaborative, LLC

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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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VITamin D and OmegaA-3 Trial (VITAL Study) https://www.vitalstudy.org/

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PIPC Partnership to Improve Patient Care

August 20, 2019

Dr. Steven D. Pearson
President
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Dear Dr. Pearson,

On behalf of the Partnership to Improve Patient Care (PIPC), we are writing to provide comments on the Institute for Clinical and Economic Review's (ICER) draft evidence report on treatments for Cardiovascular Disease (CVD). CVD kills more Americans each year than any other disease.[1] With this in mind, it is particularly important that effective treatments are available to patients. The methodological flaws in ICER's report are concerning, especially the suggestion that only 2% of eligible patients should have access to highly effective treatments, which is both unethical and illogical.

We would like to highlight the following concerns with ICER's report:

ICER's Budget Impact Threshold is Unethical and Illogical

The budget impact model explicitly states the percentage of eligible patients that could be treated in a given year, noting that only 2% of eligible patients could be treated with rivaroxaban without crossing the budget threshold and only 2% of eligible patients could be treated with icosapent ethyl without crossing the budget threshold. While ICER claims that its budget impact model is not a budget cap, its sole purpose appears to be to recommend to payers that they impede patient access as a way to limit spending on treatments. In that sense, ICER's budget threshold is indistinguishable from a budget cap on new drug spending. If ICER's true goal was to simply provide payers with information on the impact treatments will have on their budgets, no threshold is necessary.

Not only does rationing present an ethical problem by suggesting that only 2% of eligible patient should receive treatment for a disease, it is also illogical. Use of effective interventions (which even by ICER's admission, these are) leads to fewer costly adverse events and avoidable health spending, improving quality of life, and increasing productivity, both for patients and for the health system. While reductions in health care spending are certainly necessary, our goal should be to eliminate care that is less effective, and less valuable to patients, rather than applying a blunt threshold to innovative treatments.

[1] American Heart Association. Cardiovascular Disease. Accessed July 30, 2019.

It is also problematic that ICER's budget impact model assumes a take-up rate of 100% over five years for these new drugs, which assumes that every single person that could theoretically benefit from these interventions will ultimately receive it. This flawed logic has been proven incorrect time and time again, yet ICER persists in making this assumption. A prime example of this was ICER's budget impact model for PCSK9 inhibitor drugs in 2015.[2] This report also relied on the unrealistic assumption of full take-up over five years. Four years later the take-up rate of PCSK9 inhibitors is estimated to be less than 1%.[3]

ICER Incorrectly Assumes There is No Quality of Life Impact from Interventions

ICER assumes there is zero "quality of life" impact from these interventions despite a growing body of evidence that successful treatment of CVD risk factors has had strong effects on psychological well-being and quality of life beyond gains associated purely with their event risk effects, or movements across health states. The ICER model disregards these effects.

For example, a recent study in long term statin users showed lower depression, anxiety, and hostility after adjustment for the propensity for statin use and potential confounders. The beneficial psychological effects of the statins appeared to be independent of the drugs' cholesterol-lowering effects.[4] Patients with high blood pressure have seen similar results.[5]

ICER even acknowledges that there is ongoing research into quality of life through COMPASS and notes that at the time of this report the data is not yet available. It is frustrating that ICER continues to translate "yet to report findings" into "no effect," which is frequently not accurate.

ICER Uses an Artificially Narrow Definition of Major Adverse Cardiovascular Event

ICER chooses to use an incredibly narrow definition of Major Adverse Cardiovascular Event (MACE) in its base case, despite it being well known how MACE is defined and what events are included that have a significant impact on outcomes.[6] The definition of MACE in the base case is a shorthand version including only myocardial infarction (MI), stroke and CVD death. A wider and more appropriate definition of MACE that includes revascularization and unstable angina is used in the sensitivity analysis. It is unsurprising that the analysis using a full and appropriate definition of MACE shows much more beneficial effectiveness results. What is surprising is that

[2] See https://icer-review.org/wp-content/uploads/2016/01/Final-Report-for-Posting-11-24-15-1.pdf
[3] Chamberlain AM, Gong Y, Shaw KM, Bian J, Song WL, Linton MF, Fonseca V, Price-Haywood E, Guhl E, King JB, Shah RU. PCSK9 Inhibitor Use in the Real World: Data From the National Patient-Centered Research Network. Journal of the American Heart Association. 2019 May 7;8(9):e011246.
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despite these results, ICER actively chose to use the less comprehensive measure of MACE in the base case.

ICER's Model Uses Inappropriate Data for the Population Being Treated with These Drugs

The source of ICER's data comes from a CVD risk calculator constructed from the Framingham Heart Study (D'Agostino et al 2008),[7] which uses data from a less diverse population to estimate the relative risk of a series of CVD events, such as stroke, MI and CVD death than in the general population. There is detailed literature as to why this risk calculator tends to significantly underestimate risk for a more generalized population.[8] There are two key reasons this particular risk calculator is a bad fit for this research question:

1. Using this risk framework, ICER's model assesses the probability of a CVD event in a primary prevention population, whereas the drugs being evaluated are likely to be used more commonly on a secondary prevention population - those who have been diagnosed with coronary artery disease (CAD) or peripheral artery disease (PAD) or have experienced a previous cardiovascular event. The populations who are likely to benefit from these drugs are therefore likely to have much higher relative risk of future CVD events than the population used to construct the risk calculator. As a result, any absolute estimate of effect using this risk calculator will be an underestimate the absolute risk reduction for the population that is likely to benefit.
2. The risk calculator from which the ICER model is derived uses data from ages 30 to74 only, but the proportion of people being treated for CVD in the general population who are over 74 years of age is almost 50% and rising. Thus, information derived from the risk calculator does not paint an accurate picture of the patient population for which ICER is assessing treatments. In fact, the American Heart Association has endorsed aggressive secondary prevention of CVD events in adults older than 75 years of age, recognizing that the risk of several forms of atherosclerotic CVD, including stroke and MI, rise significantly with age.[9] In addition to inappropriate age representation, the study was not representative of CVD patients in terms of race or gender. The REDUCE-IT population was less than 30% female, and less than 10% people of color, thus, important populations are underrepresented. Research has demonstrated a significant racial health disparity in CVD. By failing to include data that properly reflects these subpopulations risk and likely outcomes, ICER is contributing to furthering these health disparities.

[7] D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care. Circulation. 2008 Feb 12;117(6):743-53.
[8] Jørstad HT, Colkesen EB, Boekholdt SM, Tijssen JG, Wareham NJ, Khaw KT, Peters RJ. Estimated 10-year cardiovascular mortality seriously underestimates overall cardiovascular risk. Heart. 2016 Jan 1;102(1):63-8.
[9] Kozak LJ, DeFrances CJ, Hall MJ. National hospital discharge survey: 2004 annual summary with detailed diagnosis and procedure data. Vital and health statistics Series 13, Data from the National Health Survey. Atlanta, GA: National Center for Health Statistics; 2006:1-209

The use of the Framingham Heart Study, instead of real-world data, in constructing the risk calculator had led to serious shortcomings in ICER's model. The cost-effectiveness methodology literature has been consistent over recent years in emphasizing the need to use real word data sources where possible for baseline risk data[10, 11] and for cost-effectiveness modeling,[12] not risk calculators constructed from non-representative populations such as the Framingham Heart Study,[13,14] which is far from reflective of the true risk of a generalized population. We would strongly advise ICER to change its sources for baseline risk and re-run its estimates of effectiveness and ultimately cost-effectiveness using a real world data source that encompasses the entire population of need who could benefit from such drugs, such as the one derived from the REACH registry.[15]

Conclusion

ICER continues to use a flawed methodology, ignoring real-world data and quality of life outcomes that matter to patients in favor of data that easily crosswalks into the discriminatory QALY metric. We urge ICER to reconsider both its data sources and its concerning theory that health care must be rationed to achieve savings and efficiency in our health care system.

Sincerely,

Tony Coelho
Chairman, Partnership to Improve Patient Care

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[15] Wilson PW, D'Agostino Sr R, Bhatt DL, Eagle K, Pencina MJ, Smith SC, Alberts MJ, Dallongeville J, Goto S, Hirsch AT, Liau CS. An international model to predict recurrent cardiovascular disease. The American journal of medicine. 2012 Jul 1;125(7):695-703

August 20, 2019

Steven D. Pearson, MD, MSc, FRCP
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RE: Additive Therapies for Cardiovascular Disease Draft Evidence Report

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening and life-altering conditions (such as cardiovascular diseases) to improve their access to vital therapies and services. Access is a matter of survival and quality of life for those patients, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging all stakeholders to foster realistic, people-centered, solution-oriented discussions. That is, our goal is a balanced dialogue that illuminates the truth about health care in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's March 14th Draft Evidence Report about "Additive Therapies for Cardiovascular Disease," that was released on July 24th and updated on July 30th.

At the onset we want to express our confusion about why ICER chose to do a single report about two treatment options that work through very different mechanisms of action. As is clear in the draft report, it is really two analyses conducted side-by-side, with the only connection being similar (although not identical) indications and patient populations. For example, the draft report contains the following statements:

- "Separately, we also evaluated the clinical evidence for icosapent ethyl compared to optimal medical management alone."[i]
- "Rivaroxaban and icosapent ethyl were modeled separately."[ii]
- "Modeled populations differed across interventions; results for the interventions are not directly comparable."[iii]

Furthermore, the draft report adds confusion rather than clarity by presenting information about major adverse cardiovascular events (MACEs) for the two therapies in the same table – which invites direct comparison, immediately after stating "Note that the intervention-specific incremental findings are **modeled using intervention-specific populations** and therefore **should not be directly compared across treatments**."[iv] [Emphasis added]

As a matter of guiding clinical decision making – or even informing coverage or payment decisions for ICER's primary audience of health insurance companies – would it not be more useful to have produced two separate reports?

People-Centered Perspectives

Since the primary concern of people with health problems is improving their health and function – which is most often effectively done collaboratively with – clinicians, we question why the two selected therapeutic options discussed in the draft report were not presented in the context of similar treatment options, such as other medicines in the anticoagulants and dyslipidemics classes. Doing so would provide much more useful, actionable insights for patients and clinicians. In contract, the draft report is basically a recitation of two clinical trials that were the basis for each medicine's approval by the FDA, i.e., the draft report's input data is "a single randomized controlled trial (RCT) of rivaroxaban and two references corresponded to a single RCT of icosapent ethy."[v] (COMPASS for rivaroxaban and REDUCE-IT for icosapent ethyl)

We would be extremely surprised if any clinicians will gain any insights from ICER's lengthy rehashing of those trial results and conclusions, and believe that practicing clinicians would be much, much more likely to gain knowledge about the benefits and risks of these two medicines from reliable sources such as peer reviewed journal articles or conferences that reviewed current standards of care or provided updates about treatment options for cardiovascular diseases. Similarly, any payer interested in developing coverage and payment policies for these treatment options would almost certainly want to review the pivotal trial information themselves rather than rely on ICER's review – so they could both analyze the results of those trials in the context of their own patient populations and for legal defense purposes should they be challenged about their coverage decisions or payment policies, i.e., "We reviewed an ICER report" is much less defensible than "We reviewed the published literature and information from the FDA ourselves."

Budget Impact

As we've noted several times in the past, ICER's budget impact threshold process and calculations have significant arbitrary components. Specifically, your choice of timeframes for FDA approvals was two years but is now five years (2014-2018).[vi]

We appreciate your response from a year ago that "using a one-year timeline would cause too much volatility, while using an average over three years or more might not align with current trends in policy around FDA approvals. We acknowledge that there is variability in the number of approvals but would also like to point out that health system budgets are finite and do not necessarily increase in line with the annual number of approvals. We continuously monitor approval trends and, based on our observation and analysis of these trends, will consider revisions to this metric in our next value framework update."[vii]

There are two issues concerning that response as it relates to this Draft Evidence Report's Budget Impact section that we would appreciate detailed responses to:

First, since we did not see any explanation of the rationale for changing from a two-year period to a five-year period for the average number of FDA approvals in ICER's Value Framework Assessment webpage.[viii] Given that ICER's previous assertion that a two-year average was correct, we would ask that ICER explain how ICER monitored, observed and analyzed "approval trends" to determine that a five-year average is now appropriate.

Second, the response includes the statement that "health system budgets are finite." While we agree that this is technically true in the same practical sense that the amount of water or gold on earth is finite, the implication is that those budgets are somehow fixed or pre-determined. However, in the United States – as ICER surely understands – the only health care financing budgets that are actually pre-determined are those for a select few programs such as the VA and DoD – and even for those, Congress can (and has) provided additional funding when annual appropriated amounts have been reached. In contrast, the entitlements of Medicare and Medicaid programs do not operate on fixed budgets – as much as people would like to believe or proselytize that they do.

Similarly, employer-based health plans are either self-insured or fully insured. For the former, the employer is financially responsible for health care spending at, above, or below the expected/projected/estimated costs – although they may have reinsurance that protects them from exceptional costs, either overall or for any individual. And for fully insured employers, it is the insurance company that may see a larger profit from lower spending or a loss from costs above what was projected, although, they too may purchase reinsurance to limit their financial exposure. However, reinsurance in either case does not cap or limit overall health spending, it just transfers the risk to someone else.

Therefore, please explain how "health system budgets are finite" in any practical sense when in the U.S. it is the rare exception that there is actually a fixed dollar budget. In your answer we would also appreciate your including consideration of the Congressional Budget Office's finding that for Medicare, every 10% increase in usage of prescription drugs by Medicare enrollees is expected to produce 2% reduction in spending on medical services.[ix]

We also note that the concept of a "finite budget" for spending is fictional for organization delivering care in the United States in that if their annual "budget" is exceeded, they do not just close the doors. They either use reserve funds, take out loans, or – depending on their payer mix – may actually increase their bottom line if they exceed their expenditure "budget" because they have treated more than the expected number of patients or used more intensive (and thus more highly reimbursed) care modalities. We realize that this is the situation for fee-for-service and not capitated health entities, but again, they likely can use reserve funds rather than close their doors – and any higher than expected costs in one year become rationale for increasing capitated (or other reimbursement) amounts in the following year.

On a higher level, we believe that ICER's overall Budget Threshold set of assumptions and algebra runs counter to the priorities of U.S. policymakers (e.g. Congress), patients and clinicians in that it asserts that the more treatments approved by the FDA means that each can be used less often. This is a drinking-straw diameter narrow economically driven philosophical perspective that serves only those who view health care as a wasteful activity that is drain on the economy.

<u>Additional Points:</u>

- ICER's use of language and word choices is an issue we have commented on previously, and there is a particular passage in the draft report we would like to draw attention to. On page 7 of the draft report, there is this phrasing: "The management of patients with CVD has commonly consisted of behavior modification…" We understand that in clinical language

"management of patients" is a common phrase, particularly in the context of "optimal medical management" – a term also used in the draft report. However, in the context of "behavior modification" – and some of the negative implications that such a phrase can have, we strongly suggest that pairing "management of patients" with "behavior modification" is implicitly – if not explicitly – extremely paternalistic and runs directly contrary to promoting shared decision making among patients and their care team. Considering the multi-dimensional needs of people (i.e., rather than "patients") with CVD, (including diet and exercise), that ICER reconsider its word and phrasing choices, and in the future pay much closer attention to its use of language. We are confident that ICER can accomplish this since on page 13 of the draft report there is this sentence which contains much better phraseology: "Other feedback included the need to tailor the physician-patient conversation to reflect the patient's specific situation—for example, a family history of CVD, management of comorbid conditions, or the benefits of lifestyle and behavioral changes in addition to medical management." We realize that within the echo-chamber of academic and payer health care economics such issues may easily be absorbed by the walls, but we hope this point will not fall on deaf ears.

- In the assessment of coverage policies, why did ICER not review formularies from Medicare Part D plans? We think this would be particularly important since the two medicines are both eligible for Medicare coverage, and are listed as examples in the CMS approved Medicare Model Formulary.
- On page iii of the draft report, there is reference to "Janssen Pharmaceutica." [x] We believe this is a typo since that company is located in Belgium and is part of the Research and Development division of Johnson & Johnson. We believe you meant "Janssen Pharmaceuticals, Inc." which is the division of Johnson & Johnson that developed and currently produces rivaroxaban.
- The draft report includes the assertion, "the well-established benefit-risk profile and generic availability of PPIs."[xi] We found the assertion about the "well-established benefit-risk profile" strange, particularly since no supporting evidence or citations were included. Please provide citations of evidence since our understanding is that long-term use of proton pump inhibitor medications can have significant adverse effects.[xii]

Conclusions & Recommendations

Patients Rising Now continues to follow ICER's activities and publications. As has been noted, the value of the organization's work and documents to clinicians and patients is very questionable, particularly since it often does not connect to real-world information and situations, i.e., "it is important to note that randomized controlled trial findings may not generalize or translate to observed signals within the real world (i.e., efficacy does not equal effectiveness)."[xiii]

We strongly believe that ethical analyses should not primarily rely on economic calculus (with dubious data inputs) that erect barriers to patients accessing recommended treatments, which would produce worse clinical outcomes for patients. We hope that ICER will question its own assumptions and processes as vigorously as it defends them and be as transparent as possible about its data and analytical methodologies.

Sincerely,

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

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[i] Draft report, p. 17.
[ii] Draft report, p. 41
[iii] Draft report - stated several places in notes to tables.
[iv] Draft report, p. 54.
[v] Draft report, p. 19.
[vi] https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/
[vii] ICER's response to comments provided concerning prostate cancer draft evidence report, August 24, 2018.
[viii] https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/
[ix] "Offsetting Effects of Prescription Drug Use on Medicare's Spending for Medical Services," Congressional Budget Office, November 2012.
[x] https://en.wikipedia.org/wiki/Janssen_Pharmaceutica
[xi] Draft evidence report, p.36.
[xii] "Proton Pump Inhibitors: Considerations With Long-Term Use," US Pharm. 2017;42(7)4-7, www.uspharmacist.com/article/proton-pump-inhibitors-considerations-with-longterm-use, and "Proton Pump Inhibitors: Review of Emerging Concerns," Mayo Clinic Proceedings, February 2018, Volume 93, Issue 2, Pages 240–246, www.mayoclinicproceedings.org/article/S0025-6196(17)30841-8/fulltext
[xiii] Draft report p. 62.