INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Additive Therapies for Cardiovascular Disease: Effectiveness and Value
Response to Public Comments on Draft Evidence Report

September 12, 2019

Table of Contents

#	Comment	Response/Integration
Manufacturers		
Amarin		
1.	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 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.	Given prior ICER reviews in a similar disease space and given concerns with unmeasured correlation between outcomes such as MI or stroke with future coronary revascularization or hospitalization for unstable angina, we chose to include icosapent ethyl's lifetime impact on three-point MACE in the base-case cost-effectiveness findings. We note that this decision to include three-point MACE was made prior to the model analysis plan that was published in the public domain. In many instances, the FDA's decision around a trial's primary endpoint may not be well aligned with the strongest evidence that informs lifetime costs and QALYs. The base-case incremental result was $18,000/QALY, whereas the scenario analysis that included the REDUCE-IT primary endpoint and assumed no correlation between endpoints was $16,000/QALY. We report both the base-case and scenario incremental findings so that readers may better interpret an understanding of the incremental value of icosapent ethyl.
2.	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-	Please see the Controversies and Uncertainties section of the report for concerns related to assigning a relative impact of icosapent ethyl from a total events standpoint rather than a time-to-first event. Within the model, we assumed that the relative impact on time-to-first event would also hold for all subsequent events tracked in the model. Further, we calibrated the rates of events to that observed in the REDUCE-IT trial for stroke, MI, and CV death. Thus, the model tracks not only first events, but subsequent CV events. Given the controversies, we assigned the relative impact of

#	Comment	Response/Integration
	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 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.	icosapent ethyl based on the time-to-first event for first and all subsequent events within the model. We received feedback from clinicians and other CV modelers that assuming the same relative impact to subsequent CV events was reasonable, given the available evidence.
3.	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.	We did not have access to patient-level data for this review. Prior to publishing the model analysis plan and given the available evidence, we decided that a patient-level modeling approach would not lead to anticipated differences in the average incremental findings. There are a number of published cases across different diseases that suggest patient-level modeling leads to similar average incremental findings compared to cohort-level modeling. We invite Amarin to sponsor patient-level incremental analyses in order to compare and contrast the findings.
4.	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.	We agree that there may be higher quality evidence sources for certain model inputs or that could be used to relax some of the model assumptions. However, the scope of this model exercise does not include detailed patient-level evidence generation in the eight-month review timeline. The exercise involves the team identifying best-available evidence sources. Therefore, to provide actionable critiques of the review process would involve suggesting alternative available evidence sources that are considered to be of the same or higher level of quality.
5.	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."):	Thank you for these suggestions. We have edited the wording of voting questions for clarity.

#	Comment	Response/Integration
	(3) For patients currently receiving optimal medical management including 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 including statin therapy alone? (5) For patients currently receiving optimal medical management including statins, does treating patients with icosapent ethyl offer one or more of the following potential "other benefits or disadvantages" compared to optimal medical management including statin therapy 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?	
AstraZeneca		
1.	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). 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 P2Y12 inhibitor therapy. b. The superiority of ticagrelor over clopidogrel has also been clearly stated in its indication for ACS. 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	We appreciate that there are guidelines specific to ticagrelor for certain patients under specific circumstances. We have added mention of those specific cases to our Clinical Guidelines section when it is relevant to the general primary and secondary prevention population under review in this report.

#	Comment	Response/Integration
	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.	
2.	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. Furthermore, CHARISMA failed to meet its primary endpoint; as such any subgroup analysis from this study should be considered hypothesis generating at best. 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.	We respectfully disagree with the assertion regarding whether an NMA that compares trial-defined subgroups is appropriate. As Dias et al. describe in their seminal work "Network Meta-Analysis for Decision-Making," the key concern is the comparability of the data selected, and their relevance to the "decision space" (rather than the full "evidence space"). Concerns regarding the subgroup size and failure to meet primary endpoints are unfounded; indeed, if such concerns were paramount no meta-analysis of any data would ever be undertaken. Regarding the request to remove the point estimate and credible interval around ticagrelor + ASA in our NMA results, we do not understand why ticagrelor's superiority over clopidogrel in a completely separate population and set of trials should require us to remove a result obtained in this population and set of trials.
3.	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.”	Thank you for these comments. We have updated the report.
4.	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. 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 P2Y12 inhibitor or an anti-thrombin. It is important to note that such switching between agents has never been formally studied from an	We are comfortable with the method with which the data are presented. While the most robust comparison would involve a randomized, head-to-head comparison, in the absence of such evidence clinicians must make the best use of the data that are available. As noted in our report, clinicians have called for research comparing DAPT to combination therapy with ASA and a factor Xa inhibitor (e.g., rivaroxaban) (Braunwald 2017 and Cho 2019). Furthermore, the ongoing SWAP-AC trial (NCT04006288) is currently assessing the

#	Comment	Response/Integration
	"outcomes" perspective and CHARISMA and COMPASS analyzed initiation of therapy and not switching. 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.	feasibility of switching from DAPT to rivaroxaban + ASA.
Janssen		
1.	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.	Throughout the report we have meticulously emphasized that we are not directly comparing rivaroxaban and icosapent ethyl. Evidence summaries and results are separated by intervention throughout the majority of the report. While there are places throughout the report (primarily in Section 4) where it makes sense to present results for the two interventions in parallel to avoid cumbersome repetition for the reader, in these instances we have explicitly stated that the results are not to be directly compared, either in text or with a table footnote stating, "Modeled populations differed across interventions; results for the interventions are not directly comparable."
2.	**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).	Thank you for this clarification. We have modified the text in Section 1 where we refer to the indication for rivaroxaban.
3.	**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.	We are estimating patients under the approved label, not based on the eligibility criteria of COMPASS. Additionally, we do not see how the labeled indication of "chronic CAD or PAD" affects the size of the population, since everyone with acute CAD or PAD also has chronic CAD and/or PAD.

#	Comment	Response/Integration
	o 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.	
4.	**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).	Please see our response to AstraZeneca's second comment. In addition, we are surprised at the source of this comment, given that Janssen's marketing partner for rivaroxaban outside the US submitted NMAs featuring this treatment contrast to both the Canadian Agency for Drugs and Technologies in Health (CADTH) and England's National Institute for Health and Care Excellence (NICE).
5.	**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.	Please see our response to AstraZeneca's second comment.

#	Comment	Response/Integration
6.	**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.	As clearly stated in the economic section of the report, the comparison of rivaroxaban + ASA to DAPT with clopidogrel was an exploratory scenario analysis. We ran a few scenario analyses, including assuming the same bleeding rates and we further explored the impact of differences in relative bleeding rates on cost-effectiveness estimates. Given that these analyses are scenarios and not part of the base case, their emphasis within the discussion section is minimized.
7.	**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.	We recognize the heterogeneity across stroke and other CV events. The utility or cost of a mild stroke is very different from that of a severe stroke. Interesting questions include whether the average estimates for the cost of a stroke or utility for a stroke are representative of this study population and whether the intervention may disproportionately avoid milder or more severe strokes. We conducted a weighted average approach for the utility of stroke based on the COMPASS trial proportions of stroke severity and found this weighted average estimate for utility to be higher than the average utility for stroke that we used in the base-case model. Further, within COMPASS, there was no evidence to suggest higher relative reductions in severe strokes compared to more mild strokes. Thus, the base-case findings will result in lower incremental cost-effectiveness findings compared to if we had used the weighted average estimate for stroke utility. Additionally, we have concerns about a drug reducing "fatal and disabling strokes," since cause of death from an acute intracerebral hemorrhage may be difficult to ascertain and can be ascribed to sudden cardiac death. As such, a drug that causes strokes that would have been disabling (or fatal over days) to result in rapid death from severe hemorrhage could appear to reduce "fatal and disabling strokes." If there are data showing that all patients in COMPASS who had rapid death underwent autopsy to establish the cause of death, we would reassess this concern.
8.	**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	Thank you for this comment. There are controversies related to how to monetize patient time from a modified societal perspective. We made the conservative assumption that all people within the model, no matter their age or ability to

#	Comment	Response/Integration
	Score, mRS≥3 would very likely go on permanent disability and claim Social Security Disability after Stroke (Medford-Davis 2016, Disability Benefits).	work, would be assigned the same level of absenteeism for CV events. Further, this level of absenteeism was valued based on average salary estimates for all individuals (those working as well as those who are not working). Therefore, one could argue that the estimated impacts due to indirect costs may on average, be higher than what is actually valued within society. We note that severity of CV events will impact these estimates, but we did not have evidence to suggest that the evaluated interventions had higher impacts on severe events compared to more mild events.
9.	**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.	Following standard health economic practice, we assumed that the net price of rivaroxaban would remain the same over time, as we have no way to predict price increases or decreases in the future. We did not assume any annual price increases.
10.	• 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.	ICER's potential budget impact analysis is applied to each intervention we study, regardless of the therapy area. We believe it is important to prepare for large budget impacts in the health care system, whether from treatment of hepatitis C infections, CVD, or any other condition.
11.	• 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.	The purpose of the potential budget impact analysis is to measure the marginal impact of new interventions that are being considered. When new interventions, even those that are relatively cheap, are considered for very large populations, it is important to plan for the potential impact on health care budgets. We also note that our potential budget impact analysis uses net costs that account for cost offsets from treatment as well as the cost of the treatment itself, which would need to be accounted for in any analysis of aspirin's potential budget impact. Even without estimating cost offsets for aspirin treatment, we point out that treating all 16.9 million individuals in a single year would actually generate a budget impact of $305 million assuming $18 annual price per patient, well below the $819 million per year threshold. In reality, the annual budget impact is far less than this, given that our method for estimating annual budget impact is applied to the segment of that 16.9 million that would be treated each year over five years (~3.4 million individuals).

#	Comment	Response/Integration
Patient Advocacy and Research Organizations		
Aimed Alliance		
1.	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 as a supplement to "reduce triglyceride levels in patients with severe hypertriglyceridemia" while rivaroxaban is indicated for "reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial defibrillation," and for the treatment, prevention, and reduction of the recurrent risk of deep vein thrombosis and pulmonary embolism. Therefore, we caution ICER against conducting a comparative effectiveness analysis of these two medications because they are not substitutes for each other.	The report clearly mentions throughout that our intent is not to compare icosapent ethyl and rivaroxaban to each other but rather the relevant standard of care options for each. This is described both in the summary of project scope as well as the introductory paragraph for the methods section of the evidence review (Section 3.1).
2.	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. Moreover, families of individuals who die prematurely incur the value of lost earnings. Factors such as these should be considered in ICER's analysis.	ICER does incorporate direct and indirect costs to patients in our calculations. Productivity losses are incorporated in a "societal perspective" scenario analysis in every report, including this one. However, we acknowledge that the data on these elements is often incomplete and therefore our economic analysis cannot capture all the costs and benefits important to patients. The Other Benefits and Contextual Considerations section of our reports is meant to capture what the clinical and economic data may have missed. We understand the importance of these considerations and thus have our CEPAC/CTAF panels vote on these considerations individually, and use them as context to inform their "long-term value for money" votes.
3.	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. 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	Given prior ICER reviews in a similar disease space and given concerns with unmeasured correlation between outcomes such as MI or stroke with future coronary revascularization or hospitalization for unstable angina, we chose to include icosapent ethyl's lifetime impact on three-point MACE in the base-case cost-effectiveness findings. We note that this decision to include three-point MACE was made prior to the model analysis plan that was published in the public domain. In many instances, the FDA's decision around a trial's primary endpoint may not be well aligned with the strongest evidence that informs lifetime costs and QALYs. The base-case incremental result was $18,000/QALY, whereas the scenario analysis that included the REDUCE-IT

#	Comment	Response/Integration
	were not hospitalized. 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.	primary endpoint and assumed no correlation between endpoints was $16,000/QALY. We report both the base-case and scenario incremental findings so that readers may better interpret an understanding of the incremental value of icosapent ethyl.
4.	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.	Thank you for this comment. We agree that subsequent events are important for a lifetime horizon and we included subsequent CV events within the base case and other estimates. Please see the following text in the report that details how we modeled subsequent events: "We assumed that the risk of subsequent events would be the same as that of first events even if the risk calculator suggested lower likelihood of non-fatal cardiovascular events, given the relatively high severity of the populations in the COMPASS and REDUCE-IT trials and the challenges inherent in evaluating subsequent event risks in situations with event types that are not independent from one another. Once calibrated to the trial's control arm first observed events, these same risk calculator parameters were also used in the model's treatment arm in combination with the treatment- and event-specific hazard ratios."
5.	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 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.	The QALY does not measure the value of human life. The QALY measures the value of treatments. The QALY is the gold standard for measuring how well a medical treatment improves and lengthens patients' lives, and therefore has served as a fundamental component of cost-effectiveness analyses in the US and around the world for more than 30 years. Because the QALY records the degree to which a treatment improves patients' lives, treatments for people with serious disability or illness have the greatest opportunity to demonstrate more QALYs gained and justify higher prices. Moreover, to be responsive to the concerns about the QALY, ICER now incorporates a calculation of the Equal Value of Life Years Gained (evLYG), which evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. More information can be found here: https://icer-review.org/material/the-qaly-rewarding-the-care-that-most-improves-patients-lives/.
6.	While clinical trials have provided evidence of the safety, effectiveness, and value of icosapent ethyl for the	We are unsure how a report that states that a treatment brings better clinical benefits at a

#	Comment	Response/Integration
	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.	reasonable price could be used to deny care. On the contrary, as stakeholders anticipate FDA approval, they have a rigorous and independent report to reference during the time when pricing, coverage, and practice policies are being decided. This report is a tool that can be used to help achieve fair pricing and fair access for patients, manufacturers, payers, and providers—all of whom will be making policy decisions as soon as the FDA issues its decision, with or without mature data.
Medical Research Collaborative		
1.	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.	We are unaware of the source of the statement attributed to Dr. Bhatt regarding an actual relative risk reduction of 20%. We also note that, over wide ranges of relative risk for MI, stroke, and CV death, the cost-effectiveness of icosapent ethyl ranged between $12,000 and $27,000 per QALY gained (see Figure 4.3 in the report).
2.	The increase in LDL-C in the 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.	While this is an interesting supposition, the conclusion is highly speculative and not informed by any data available from REDUCE-IT.
3.	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 the make the sharp increase in placebo group that occurred despite this tendency, noteworthy.	See comment above.
4.	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. However, with a trial as large as REDUCE-IT, and	While log-transforming hs-CRP data may have been unnecessary, we note that the results are consistent in both the untransformed and log-transformed analyses (i.e., statistically-significant reductions from baseline to year two in the icosapent ethyl group).

#	Comment	Response/Integration
	with nine separate fasting lipid panels performed on average per subject to ascertain levels, log-transforming these biomarker data is unnecessary...	
5.	If MO (mineral oil) 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?	Please see our response to your second comment.
National Forum for Heart Disease & Stroke Prevention		
1.	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.	Please see our first response to Aimed Alliance regarding presentation of the comparisons of interest in the report.
2.	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.	ICER is dedicated to conducting evidence evaluation and synthesis that meet the most rigorous standards of integrity, and thus makes every effort to meticulously note areas of uncertainty in the evidence or issues that are beyond the scope of our review. We feel we have done so in this report. If the National Forum has specific concerns about where we may have fallen short, we are eager to correct those mistakes and welcome specific feedback.
3.	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.	Thank you for this feedback. We are working on ways to share our models with stakeholders, while also preserving the intellectual property of our academic collaborators. We do, however, offer each manufacturer the opportunity to review the model during the public comment period. Both manufacturers in this review participated and neither submitted any concerns or comments on the design.
4.	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	Thank you for these estimates and references. We will update the report accordingly.

#	Comment	Response/Integration
	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.	
5.	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 QALY is the gold standard for measuring how well a medical treatment improves and lengthens patients' lives, and therefore has served as a fundamental component of cost-effectiveness analyses in the US and around the world for more than 30 years. Because the QALY records the degree to which a treatment improves patients' lives, treatments for people with serious disability or illness have the greatest opportunity to demonstrate more QALYs gained and justify higher prices. Moreover, to be responsive to the concerns about the QALY, ICER now incorporates a calculation of the Equal Value of Life Years Gained (evLYG), which evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. More information can be found here: https://icer-review.org/material/the-qaly-rewarding-the-care-that-most-improves-patients-lives/.
6.	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.	We do not intend for any direct comparisons to be made across the two evaluated interventions. All results tables within the cost-effectiveness analysis section of the report include a footnote that addresses this concern.
7.	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.	Please see our second response to AstraZeneca as well as our fourth response to Janssen.
8.	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	We disagree. We think these statements accurately reflect the state of knowledge regarding combining these treatments with each

#	Comment	Response/Integration
	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.	other or with a PCSK9 inhibitor. All stakeholders should be clear on the available evidence when making evidence-based decisions about care.
9.	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.	We acknowledge that our model does not capture all possible costs to patients and society. As you noted, we conduct scenario analyses to help show the range of these costs so decision makers can use this as context. One reason that we do not make the modified societal perspective our base case is because including productivity losses results in a model that favors treating people of working age (since they can incur productivity losses) and disadvantages providing treatment for children and the elderly. This is ethically concerning to us, as we know it would be to National Forum.
10.	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.	We have described the STRENGTH trial in a table of ongoing trials in the appendix of our report. We do not think this entry is likely to confuse stakeholders, as there is not yet sufficient detail available from the STRENGTH trial to permit any kind of comparison with REDUCE-IT. We also note, however, that the AHA's recent Science Advisory on Omega-3 Fatty Acids for the Management of Hypertriglyceridemia anticipates that the results of the STRENGTH trial are "likely to further inform prescribing decisions." This trial may provide additional evidence to support or challenge the hypothesis that the positive results from REDUCE-IT may be due to the purified EPA-only formulation of icosapent ethyl.
11.	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,	The analysis looked at medication discontinuation rates from the clinical trials, though it is certainly true that adherence is typically better in clinical trials than in the real world. For the first comment mentioned, we explicitly heard this from patients and clinicians. For the second, there are clearly issues with acceptance and adherence with injectable therapies like PCSK9s and because of

#	Comment	Response/Integration
	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.	concerns about adverse effects with statins. We do not think these statements conflict in any way.
12.	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.	ICER's potential budget impact threshold is explicitly not a "rationing framework," but instead is intended to raise an "affordability and access alert" in specific cases where the potential budget impact is likely to be large. Its purpose is to allow payers and others to plan for the potential budget impact so that appropriate access can be maintained. This type of planning may be especially important in conditions that are very common, where the large number of patients eligible for treatment can lead to large spending increases even when treatments are considered cost-effective
13.	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.	We share your concern about the number of drugs that are not cost-effective at the price chosen by their manufacturer. In cases where manufacturers choose prices in alignment with value, even if the price tag is a high dollar amount, our analysis shows the drug to be cost-effective. Notably, ICER recently reviewed Zolgensma, a life-saving treatment for children with spinal muscular atrophy. This drug is considered to be most expensive drug to ever hit the market with a $2.1 million price tag and our analysis found it was cost-effective at that price. Payers and others need to be made aware of cost-effective drugs that have potentially large budget impacts so that policy decisions can be made around how to ensure access to such therapies.
14.	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,	Our analysis does not suggest constricting access to treatment, but simply points out that budget-holders may need to plan for increases as more

#	Comment	Response/Integration
	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.	patients receive treatment, to ensure that there is appropriate access to cost-effective treatments.
15.	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.	ICER's budget impact threshold is not based on WHO calculations. It links growth in health care spending to growth in GDP. Maryland has a long-standing arrangement that limits hospital cost growth to the growth rate estimated for the state's overall economy. Massachusetts already links policy actions to growth in health care costs that outstrip growth in the state per capita GDP, and recent initiatives may extend state oversight to prescription drugs as well.
16.	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.	The potential budget impact calculations used estimates of the prevalent population with CAD, with the understanding that incident acute cases that survive will become prevalent (chronic) cases. Our analysis does not assume that any specific percentage of eligible patients will receive treatment, but looks at the hypothetical budget impact if increasing numbers of patients eligible for a treatment were to receive it. As stated above, its purpose is not to ration care, but to allow for budget planning.
17.	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.	See our response above.
Partnership to Improve Patient Care		
1.	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	ICER's potential budget impact threshold is explicitly not a budget cap, but instead is intended to raise an "affordability and access alert" in specific cases where the potential budget impact is likely to be large. Its purpose is not to "impede patient access," but to allow payers and others to

#	Comment	Response/Integration
	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.	plan for the potential budget impact so that appropriate access can be maintained.
2.	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.	Our analysis does not suggest that only 2% of patients should receive treatment, but points out that budget-holders may need to plan for increases as more patients receive treatment. We would also point out that our analyses use net costs that account for cost offsets from fewer adverse events and avoided spending, as well as changes in quality of life.
3.	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.	Our analyses do not assume that 100% of patients will receive treatment, but look at the hypothetical budget impact if all patients eligible for a treatment were to receive it.
4.	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... 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.	It would be unusual to consider it an enhancement to quality of life to be taking additional medications that have side effects; this seems like the very definition of being over medicalized. We do not think manufacturers should charge for benefits they have not yet demonstrated.
5.	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. 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 despite these results, ICER actively chose to use the less comprehensive measure of MACE in the base case.	Given prior ICER reviews in a similar disease space and given concerns with unmeasured correlation between outcomes such as MI or stroke with future coronary revascularization or hospitalization for unstable angina, we chose to include icosapent ethyl's lifetime impact on three-point MACE in the base-case cost-effectiveness findings. We note that this decision to include three-point MACE was made prior to the model analysis plan that was published in the public domain. In many instances, the FDA's decision around a trial's primary endpoint may not be well aligned with the strongest evidence that informs lifetime costs and QALYs. The base-case

#	Comment	Response/Integration
		incremental result was $18,000/QALY, whereas the scenario analysis that included the REDUCE-IT primary endpoint and assumed no correlation between endpoints was $16,000/QALY. We report both the base-case and scenario incremental findings so that readers may better interpret an understanding of the incremental value of icosapent ethyl.
6.	The source of ICER's data comes from a CVD risk calculator constructed from the Framingham Heart Study (D'Agostino et al 2008), 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. 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. 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%	This comment is not accurate. The following text describes our approach: "CV events included in the base-case model were: MI, stroke, and CV-related mortality. Validated cardiovascular risk calculators were used to estimate time-varying annualized event rates within the control arm (Table 4.4). The control arm's 10-year risk of cardiovascular events was calibrated such that the model produced consistent first CV events observed over the same period as within the trial." Therefore, we only used the Framingham Heart Study to help project the trial-based calibrated events over time horizons beyond the trial durations. The Framingham Heart Study only impacted the control arm's event rates based on small changes in the cohort's characteristics over time such as age. The relative impact of the interventions of interest were solely based on the trial evidence (not the Framingham Heart Study). We agree that it would be beneficial if manufacturers of new therapies included more diverse populations in their clinical trials, but we are uncertain how ICER could be expected to do anything other than report on the results of the trial as it was actually performed.

#	Comment	Response/Integration
	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.	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 , and for cost-effectiveness modeling, not risk calculators constructed from non-representative populations such as the Framingham Heart Study, , 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.	As mentioned above, the Framingham Heart Study had little impact in the cost-effectiveness findings. The primary evidence drivers in these cost-effectiveness analyses were the trial-based relative reductions in CV events, costs and disutility of CV events, and the net price of the interventions. The trial-based relative risk signals are the most important model inputs related to uncertainty in model outputs as depicted in the one-way sensitivity figures. That said, we do not understand the comment, "[t]he use of the Framingham Heart Study, instead of real world data...." The Framingham Heart Study is one of the longest and largest examples of a study generating real world evidence.
Patients Rising Now		
1.	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."** [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? 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	We are deeply grateful to Patients Rising Now for its suggestions on how to improve the usefulness and efficiency of ICER reports. Patients Rising Now clearly recognizes that ICER, like all organizations, groups, and societies, must work within a constrained budget to maximize its utility for stakeholders. We believe this strategy carries over into other domains as well.

#	Comment	Response/Integration
	trial (RCT) of rivaroxaban and two references corresponded to a single RCT of icosapent ethyl." (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."	
2.	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. 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.	ICER recalculates the potential budget impact threshold each calendar year, using the most recent inputs available. In the recalculation of ICER's potential budget impact threshold for calendar year 2019, we extended the time period over which we average the annual number of drugs approved by the FDA from two to five years to reduce fluctuations in the threshold due to this variable, as the number of approvals varies widely from year to year.
3.	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.	Pointing out that health systems budgets are finite in no way implies that they are fixed or pre-determined. In fact, the next phrase in that sentence explicitly mentions changes in budgets (that "do not necessarily increase in line with the annual number of approvals"). Even though budgets are not fixed or pre-determined, that does not mean that we never have to worry about the rate of increase in budgets or their sustainability over time.

#	Comment	Response/Integration
4.	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.	Thank you for your comment. We have revised the language to avoid any paternalistic overtones, as this was certainly not our intent.
5.	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.	Thank you for this suggestion. We added discussion of a national Aetna Medicare plan to the report.
6.	On page iii of the draft report, there is reference to "Janssen Pharmaceutica." 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.	Thank you for this comment. We have made this correction.
7.	The draft report includes the assertion, "the well-established benefit-risk profile and generic availability of PPIs." We found the assertion about the "well-established benefit-risk profile" strange, particularly since no supporting evidence or citations were included. Please	We will add relevant citations to the report. Of course, a "well-established benefit-risk profile" does not preclude the possibility of long-term adverse effects if they are well-documented (which they are). The most important citations are

#	Comment	Response/Integration
	provide citations of evidence since our understanding is that long-term use of proton pump inhibitor medications can have significant adverse effects.	currently already in the report (i.e., guideline recommendations for routine use of PPIs in patients receiving anticoagulants plus aspirin).