

December 9, 2020

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for High Cholesterol. Cardiovascular disease (CVD) is one of the leading causes of death in the United States. Between 2013 and 2016, 12.5 million Americans experienced CVD, and between 2014 and 2015 direct and indirect costs CVD and stroke were \$351.3 billion.¹ One of the major risk factors for CVD is high cholesterol. Given this large and growing human and economic cost, it is essential to ensure access to effective treatments for high cholesterol, particularly for patients who cannot tolerate statins. Therefore, PIPC encourages ICER to consider the following comments.

The model is not reflective of the indicated population

The risk of major adverse cardiovascular events (MACE) is much higher in African Americans,² and African Americans make up a disproportionate share of those who have atherosclerotic cardiovascular disease (ASCVD).³ Despite this reality, the randomized controlled trials (RCTs) used to provide estimates of effectiveness in the ICER model were predominately populated by white individuals. For example, in CLEAR Wisdom 94% of recruited patients were white, ORION 11 was 98% white, and CLEAR Harmony was 96% white.

The RCT population also does not reflect the age of actual patients. The median age of the patients in the referenced trials was 64 years, with fewer than 8% over 70 years. In reality, we know that almost half of people on lipid-lowering medication are over 70.

While ICER cannot control the recruitment of people into trials, it can use the modeling process to effectively translate evidence from RCT populations into real-world populations and evaluate them in a way that provides valuable insights into the relative value of these drugs across

¹ American Heart Association, 2019, www.heart.org/-/media/files/about-us/statistics/2020-heart-disease-and-stroke-ucm_505473.pdf?la=en.

² Rosamond WD, Chambless LE, Heiss G, Mosley TH, Coresh J, Whitsel E, Wagenknecht L, Ni H, Folsom AR. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987–2008. *Circulation*. 2012; 125:1848–1857

³ Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, De Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR. Heart disease and stroke statistics—2017 update.

communities, rather than over-relying on an “average” American.⁴ It should also make every effort to highlight the importance of running analyses of key subgroups of interest, such as underrepresented communities and communities that have a disproportionately high burden from the disease being addressed.

Wider sets of subgroup analyses are justified as the results from RCTs show considerable heterogeneity of effect

The ICER model uses a composite estimate of relative effectiveness but there was significant heterogeneity between trials (heterogeneity among these studies was high and statistically significant ($I^2=69%$, $p<0.01$)).

The percentage reduction in LDL-C appears to be greater in the statin-intolerant trials compared with trials where patients were on background statin therapy (21-28% versus 17-19%). Even when broken down into two groups of (A) patients with ASCVD/HEFH and (B) patients with statin intolerance, the latter group estimate had an I^2 statistic of 75%. In fact, the heterogeneity was higher than in the overall sample. This is usually an indication that subgroups should be broken into even more granular groupings to get reliable estimates of effectiveness.

Therefore, we would highly encourage ICER to run additional subgroup analyses, as further investigation may show the drug to be more or less effective in different populations as defined by race, age, or baseline risk. This is highly valuable information for patients and providers in making treatment decisions.

ICER makes some incorrect assumptions about ACSVD patients

The LDL-C levels used are lower than one would see in a real-world population. ICER’s assessment uses a starting LDL-C of 88 mg/dL. This is very low for someone who requires lipid-lowering medication. Someone with high cholesterol is typically defined as having an LDL-C level above 120 mg/dL.

ICER also underestimates the percentage of the population that cannot tolerate statins. ICER assumes statin intolerance has a prevalence of 10% but real-world estimates estimate prevalence at up to 20%.⁵

⁴ Basu A, Grieve R, Pritchard D, Stevens W. One size does not always fit all in value assessment. *The American journal of managed care*. 2009;25(11):540-2.

⁵ Handelsman Y, Jellinger PS, Guerin CK, et al. Consensus statement by The American Association of Clinical Endocrinologists and American College of Endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm 2020 executive summary. *Endocrine Practice* 2020;26(10):1-29.

Voting questions should appropriately align with the assessment

The majority of the voting questions regarding ASCVD are general rather than being tailored towards the four subpopulations defined by ICER in this assessment. ICER's findings varied significantly across the four populations. In order to accurately depict value to each of these subpopulations, we would strongly recommend ICER adjust the questions and probe voting panel members on issues specific to each of the four subpopulations.

ICER conflates the DALY and QALY, which are not compatible, in this model

The sources of health utilities for the model are not derived from patient reported outcomes considered to be standard. The model uses Disability-Adjusted Life Year (DALY) weights that have not been generated by patients at all.^{6,7,8} Although the QALY and the DALY look very similar, they are in fact different. One measures health states and one measures disease states. The DALY is largely seen as a measure of disease burden – most commonly used in developing countries,⁹ whereas the QALY is a measure of health gain. The two metrics are not interchangeable, and as such alternative interventions measured using a QALY will not be comparable to estimates developed using the DALY.

The use of DALY weights, rather than HSUVs, significantly undervalues the burden of disease states and CV events

Putting aside the point that the source for health state utility values (HSUV) used to calculate QALYs are not in fact health state values calculated for the QALY, it is also worth noting the paucity of the actual numbers being used. The DALY weights used in the model, such as History of Angina, and History of ACS are estimated at between 0.88-0.96 (Table 5.4). These are “utility values” that are higher than most “healthy” states in most cost-per-QALY models.

For context, a recent review of HSUVs (using the more traditional EuroQOL 5-dimension method)¹⁰ shows that HSUVs for history of angina range from 0.615-0.775, HSUVs for history of stroke range from 0.626-0.668, and HSUVs for history of heart attack range from 0.721-0.742.

⁶ Moran AE, Forouzanfar MH, Roth GA, et al. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. *Circulation*. 2014;129(14):1493-1501.

⁷ Moran AE, Forouzanfar MH, Roth GA, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation*. 2014;129(14):1483-1492.

⁸ Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* (London, England). 2012;380(9859):2197-2223.

⁹ Sassi F. Calculating QALYs, comparing QALY and DALY calculations. *Health policy and planning*. 2006 Sep 1;21(5):402-8.

¹⁰ Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in Health*. 2010 Aug;13(5):509-18.

ICER includes lifetime health care costs unrelated to ASCVD

ICER's model includes all lifetime medical costs, including those unrelated to ASCVD. Modeling of medical costs unrelated to the disease in question is uncommon.

Beyond the inconsistency in modeling of these costs when ICER has not typically included them in its past models (with the exception of its COVID-19 model), the logic and implementation of ICER's inclusion of these costs raises questions. The incorporation of such costs introduces a questionable incentive structure for the analysis. Even if a manufacturer were to offer a life-saving therapy for free, inclusion of these costs would raise the question of whether it is worth providing life-saving treatment to a patient given that they will go on to incur medical costs unrelated to the clinical decision in question. This would mean only treating patients who never get sick again in their lifetime would have value, a decision process that is not desired in any healthcare system.

Also, while ICER includes these unrelated healthcare costs for all surviving patients, these patients' contributions to the healthcare system are excluded. For example, surviving patients may incur medical costs, but they also may pay premiums, deductibles, and co-pays to their insurance payer, which then pays for the medical costs. Similarly, surviving patients may pay or have paid taxes that fund their insurance (e.g., Medicare and Medicaid).

Conclusion

ICER continues the concerning trend of looking to an "average" patient, instead of determining value to the relevant patient populations in question. We encourage ICER to revise its model to be reflective of the actual patient population and to segment voting questions to determine value to subgroups.

Sincerely,



Tony Coelho
Chairman
Partnership to Improve Patient Care