PIPC Partnership to Improve Patient Care

September 15, 2021

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 mavacamten for Hypertrophic Cardiomyopathy (HCM). HCM is a chronic disease that tends to become worse over time leading to lower quality of life for patients and long-term complications. The disease can often limit patients' ability to maintain their normal lifestyle, including being an impediment to work and caring for children. HCM is also the most common reason for sudden cardiac death in adults under 35.[1] There are currently no disease-specific medications for HCM and treatment often focuses on symptom management. Given the huge impact HCM has on patients and lack of appropriate treatments, it is essential that ICER strongly consider the needs of patients with the condition and the efforts of clinicians who treat HCM to help patients access effective treatment options as it conducts its assessment. PIPC requests ICER consider the following comments.

ICER's assessment was conducted before the completion of ongoing studies into the long-term effectiveness of mavacamten.

PIPC has often commented that ICER's assessments are conducted at too premature a stage to have a full understanding of the effectiveness and utilization of the treatments in question. ICER's mavacamten report is one of the most concerning examples of this to date. The FDA is not scheduled to make a decision regarding mavacamten until 2022, and studies into the treatments' efficacy are still ongoing. Though ICER acknowledges that the results from EXPLORER leave little or no doubt of the significant improvements on most clinical and patient reported outcomes, ICER classifies the evidence as promising but inconclusive. This classification is stated to be based on the belief that there is little long-term evidence of safety and efficacy. This is concerning, as ICER would have longer term evidence to support its conclusions if it had waited until the conclusion of ongoing trials, which it chose not to do. We would encourage ICER to postpone completion of this report to incorporate this additional data currently being collected.

ICER chose not to incorporate key outcomes requested by patients and clinicians in constructing its model.

[1] The American Heart Association. *Hypertrophic Cardiomyopathy*. Accessed August 25, 2021.

For many with HCM, the burden of disease can be severe. In addition to the risk of sudden cardiac death for most HCM patients, many patients also develop *exertional* symptoms limiting day-today functioning.[2] As a result of these symptoms, patients with HCM also face anxiety, depression, concerns about activities of daily living and social activities. Current treatments for HCM, such as beta-blockers and calcium channel blockers, are also associated with reduced ability to function in day-to-day life and reduced health-related quality-of-life (HRQOL).[3]

Given these realities, patients have emphasized that overall disease burden and variation is not well described by New York Heart Association (NYHA) class. Clinical experts expressed additional concerns with limiting the defining of the extent of disease by NYHA class alone. As such, both patients and clinicians preferred objective patient-reported outcomes as an indicator of severity and progression.[4]

Despite this perspective from patients and clinicians, the ICER model is driven solely by transition between NYHA classification categories.

ICER's model oversimplifies HCM.

ICER's model oversimplifies the experience of HCM patients by looking at a minimal number of broad health states. ICER's model looks only at transition between three categories: NYHA I, II, and III/IV. If the therapy in question is efficacious, people who remain in the same broad health state they started in at the beginning of a cycle may experience an improvement above those who are not treated which is not represented in the conclusions. Minimal broad health states often fail to capture these improvements because the distribution between and across health states will not match perfectly. Often these incremental improvements are very valuable to patients, and an oversimplified model, as ICER has constructed in this assessment, fails to capture them. Literature has shown that this type of dichotomization or over-categorization of outcomes has been shown to lead to underestimation of treatment effects.[5,6]

ICER relies on utilities constructed from randomized clinical trial (RCT) data.

There are numerous limitations in using utility data derived solely from the trial setting, and numerous studies have highlighted the utilities generated in RCTs are generally much higher than the equivalents would be for a real-world population.[7]

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[2] Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA. 1999; 281(7):650-655

[3] Jain, SS, Li, SS, Xie, J, Sutton, MB, Fine, JT, Edelberg, JM, Gao, W, Spertus, JA, Cohen, DJ, Clinical and Economic Burden of Obstructive Hypertrophic Cardiomyopathy in the United States. *Journal of the American College of Cardiology*. 2021:*77*(18_Supplement_1);668-668.

[4] (HCMA) HCA. The Voice of the Patient Report for Hypertrophic Cardiomyopathy (HCM). https://4hcm.org/wp-content/uploads/2021/06/Voice-of-the-HCM-patient-Report-finalJanuary-9-2021.pdf. Published 2021. Accessed 09/01/2021.

[5] Altman DG, Royston P. The cost of dichotomising continuous variables. Bmj. 2006 May 4;332(7549):1080.

[6] Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Statistics in medicine. 2006 Jan 15;25(1):127-41.

[7] Villines TC, Cziraky MJ, Amin AN. Awareness, knowledge, and utility of RCT data vs RWE: results from a survey of US cardiologists: real-world evidence in clinical decision making. Clinical Medicine Insights: Cardiology. 2020 Sep;14:1 179546820953410.

RCT populations are generally much healthier than real-world disease-specific populations.[8] There are always explicit and implicit exclusion criteria for recruitment into trial settings,[9] including age, the existence of co-morbidities[10] and levels of healthcare access and utilization, that make RCT populations rarely representative of real-world populations of need.[11, 12]

In addition, utilities in RCTs tend to be inflated compared to non-RCT samples of patients[13] as EQ5D gains are often generated for patients in RCTs that are non-disease or treatment-related socio-emotive components, which come as a result of receiving greater care and attention from healthcare professionals. Accompanying this is the concurrent problem of the placebo effect from patients in both arms of the trial.

As ICER shows in its sensitivity analysis, the most significant drivers of the relative cost-effectiveness of mavacamten are the health utilities used for NYHA classes. As can be seen in figure 4.2 of its draft report - small changes in the utility used to represent for NYHA class II or III/IV would potentially make mavacamten cost-saving. With this in mind, the choice of utility source has a significant outcome on the overall assessment.

The model assumes no patients discontinue use of mavacamten.

The model construction is concerning, as it assumes no health benefit after 32 weeks of treatment yet assumes cost of the drug for the remainder of that patient's lifetime. In reality, if there were no additional benefit after 32 weeks then a physician would likely stop prescribing the drug, so the overall cost would be significantly less. If the treatment is assumed to be needed to maintain the health benefit gained from the initial 32 weeks, then that should be factored into the model reflecting the health gain from the counterfactual of being taken off treatment.

It is also worth noting that in a real-world setting, there will be discontinuation in some patients. The model assuming all indicated patients remaining on this drug for their lifetime is certainly an overestimation of actual utilization.

ICER continues to rely on the discriminatory QALY.

PIPC would like to reiterate the point it has made to ICER in past comment letters that the use of the Quality-Adjusted Life Year (QALY) is inappropriate in assessing treatments for chronic illnesses. The QALY is known to discriminate against those with disabilities and chronic illnesses,[14] like HCM. We

[8] Mitchell AP, Harrison MR, Walker MS, George DJ, Abernethy AP, Hirsch BR. Clinical trial participants with metastatic renal cell carcinoma differ from patients treated in real-world practice. Journal of oncology practice. 2015 Nov;11(6):491-7.
[9] Knepper, T.C. & McLeod, H.L. When will clinical trials finally reflect diversity? *Nature* **557**, 157–159 (2018).
[10] Unger, J.M., Hershman, D.L., Fleury, M.E. & Vaidya, R. Association of patient comorbid conditions with cancer clinical trial participation. *JAMA Oncol*. **5**, 326 (2019).
[11] Mishkin, G., Arnaldez, F. & Percy Ivy, S. Drivers of clinical trial participation—demographics, disparities, and eligibility criteria. *JAMA Oncol.* **5**, 305–306 (2019).
[12] Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials. 2015 Dec;16(1):1-4.
[13] Bradburn MJ, Lee EC, White DA, Hind D, Waugh NR, Cooke DD, Hopkins D, Mansell P, Heller SR. Treatment effects may remain the same even when trial participants differed from the target population. Journal of Clinical Epidemiology. 2020 Aug 1;124:126-38.
[14]https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf

encourage ICER to look to more innovative methods to assess value that do not immediately put treatments for those with disabilities and chronic illnesses at a disadvantage.

Conclusion

ICER's model underestimates the wider burden of HCM and does not appear to have the granularity required to adequately evaluate interventions for this population. We would encourage ICER to listen to the feedback it received from patient and clinician stakeholders and to broaden its model beyond just NYHA classes.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care