

ICER PUBLIC COMMENT HYPERTROPHIC CARDIOMYOPATHY

MY STORY: Today is 9/11/21, and I would like to share my HCM (Hypertrophic Cardiomyopathy) story. I am a 62 year old female living in Missouri, and have had HCM symptoms since grade school. This disease has negatively affected my life in so many ways, and the key note in this is: **that medical science has very little hope (and absolutely no cure) to offer to me without a heart transplant.**

Growing up as a grade school aged child I had to deal with and struggle with feeling inferior to my peers as I would become SOB (short of breath) upon exertion and could not keep up or do the physical things which they could do. It was an emotional struggle where I felt very alone. I always feared P.E. class. I felt inferior, my performance was inferior, it wasn't just a feeling...it was the truth. When deciding about college, at that time, to get a B.A. degree, it was required to take a P.E. class in college and I learned that they required students to run a mile, so that was not an option for me as far as I was concerned. You see, I was not diagnosed with HCM at that time, but my maternal aunts and uncle were 'stroking out' and having cardiac issues with arrhythmias, and none of them had been diagnosed with HCM at that time either! (It ended up that my mother and all of her five siblings had this hereditary curse.) The SOB upon exertion has become a staple my entire life, which has worsened with age. Once I was into adolescence, the heart palpitations started. My mother was experiencing these as well at that time. Her siblings, located both in the Pacific NW and the eastern USA were being tested and going to different cardiologists as well for their symptoms. It took many years and many doctors with many family members, to get to the point of having a name for what plagued the family. Meanwhile, we called it the "Cutchall Curse." (Surname in the maternal bloodline.) My youngest aunt went to OHSU in Portland, OR and they tested her for Amyloidosis (it was negative) and never came up with the HCM diagnosis. After we did get the name for the "curse," my mother went from Missouri to Johns Hopkins for a cardiac evaluation and told them of HCM and they would not diagnose her with it. I have the report.

For me, regular palpitations and SOB upon exertion were my crosses to bear. I first went to a cardiologist in my 20's and had an echo (echocardiogram) and Holter monitor after Holter monitor. The Holters did show some abnormal rhythms, but nothing conclusive and no answers for the SOB. I felt like a freak and it was my silent daily struggle. Meanwhile, I continued living a life of FAKING NORMAL. I could not do the physical activities (that required exertion) of my peers, I could not have the same dreams and aspirations of my peers. Their dreams and aspirations were unlimited. Mine were limited. I had to 'go with' a desk job. I felt very held back. I remember lying awake at night with my finger on my wrist feeling my pulse and the skipped beats and wondering if I was going to die that night with my husband lying next to me and my two children in their beds, and I'd lie awake wondering if I would get to finish raising my sons

I was a faking-normal person, trying to work more than one job, raise my children and helping my mother and feeling alone with no firm answers. My mother and her siblings struggled with atrial fibrillation; only one of her five siblings received an ICD. The rest all stroked as they were not anti coagulated. I became my mother's self-educated medical

liaison as she had cardiac ablations, multiple, multiple cardioversions, multiple thoracentesis, TEE tests, an ICD (implantable cardioverter defibrillator) implanted, and two open-heart valve surgeries, all without an HCM diagnosis. Improperly diagnosed. Her left atrium was so enlarged that she started having difficulty swallowing. I have her chest xray in my possession that shows the atrium pressing up against and kinking her esophagus. My mother had memory problems due to improper blood flow to her brain due to her cardiac issues. My mother's valve repair failed after a few years and she needed a valve replacement. She was never offered a heart transplant and we didn't think to ask. In retrospect, why should we have to ask? After that second open heart surgery my mother stroked 5 1/2 months later. Not a stroke from throwing a clot like her siblings, but a brain bleed from her INR being required to be so high for the first six months after her second valve surgery. I watched her die in a hospital bed as her brain filled with blood. I have her medical records and there is no mention of HCM in them except for that Johns Hopkins report from when she was younger, asking them to look for HCM. Since I am gene positive, I had to get the gene from her. There are no cardiac issues on the paternal side of my family.

After we had the HCM name, I started getting screening echoes (looking for structural changes) every five years. (It was a cardiologist in Portland, OR who diagnosed my youngest aunt correctly, finally, a name for all of the family deaths, strokes and suffering. He instructed all family members to be screened with echocardiograms every five years.) The year 2000 brought a blow to the family with the first HCM death in my generation. A cousin two years older than me, who had been very symptomatic for years, died from SCD (Sudden Cardiac Death) in his kitchen while the paramedics were on the way, he was 43 and left a wife and two young children. Two years later, another cousin, one who was my age (43 y/o in 2002) also died of SCD in his hospital room. Neither of these cousins had been offered an ICD. The cousin my age was told that the only thing available to cure his cardiac issues was a transplant but nothing was done about it.

Meanwhile, with aging, my symptoms worsened, mainly arrhythmias and shortness of breath. I could not keep up in bicycle riding, playing basketball, and all activities that would require exertion like swimming and dancing too. I could not exercise like a normal person. Zumba and aerobics were not in my vocabulary. One situation that was insulting to me was when we went boating with my inlaws. At the end of being on the water, my inlaws and I were dropped off at the boat ramp to retrieve the boat trailer from the parking lot. Where are lakes located? AT THE BOTTOM OF HILLS. We had to walk up a hill to the parking lot. My obese and elderly inlaws (in their upper 60's) were way ahead of me walking up the hill as skinny-me struggled, running out of air and having to stop to rest to catch my breath and get my heart rate down!

In 2010 I went to a cardiologist at the renown hospital in the Midwest where my mother had had her heart valve surgeries by the #2 valve surgeon in the USA (we were told). I gave my familial HCM information, even providing copies of echo results from multiple family members, and told of the SCDs in the family. He had me do my first stress echo (exercise echo), and I lasted less than 3 minutes on the treadmill and the nurses were freaking out. Due to this, he immediately scheduled a left cardiac cath, which I passed

with flying colors. I then determined that they were not educated about HCM and were looking for cardio-vascular disease. Following all of my testing, I asked why I got SOB upon exertion now, and also since I was a child, and that cardiologist told me that when I stopped exerting, that my heart chambers continue to expand.

My oldest sister had been struggling with cardiac issues since she was in grade school as well, and she was told she had a heart murmur and was put on Inderal as a teenager. Her symptoms "exploded" in her 40's. (So many cardioversions, rides in ambulances, Air-Vac'd, etc., much of it as a widow, and with having no (adult) children, and living 2000 miles from her family. She did this alone.) Last year at the age of 66 she was in End Stage Heart Failure and was panting to walk from her living room to her bathroom. She worked for years to get on the transplant list. In Sep 2020 she received a heart transplant. The first person in our family to receive one.

I made the decision to have my screening echoes in greater frequency, every two years, once I got into my 50's. During one of these echoes, the tech saw on the echo order that it was a screening for HCM. She had a friend with HCM and was familiar with it. She told me about an HCM specialist in the Midwest not far from me. I kept his info. About this time Facebook was introduced to me and I learned of the HCMA (Hypertrophic Cardiomyopathy Association) and Lisa Salberg, the founder. This is where my main education concerning HCM started. Once my palpitations turned pre-syncope (I was in a store when the first pre-syncope event happened which brought me to my knees, as I almost passed out), I went to the HCM cardiologist specialist and he told me that he was quite sure I had HCM, but he could not diagnose me with it yet. He ordered a 30-day Event Monitor and recommended gene testing. The monitor gave names to my palpitations. Some of them felt different than others, and I kept a log of what I felt and the time/date, and when the results came back I compared them with my log, and then I had the real name of the arrhythmias. I learned I had many different kinds, but the one that would make me pre-syncope was called Non-Sustained V-Tach, and it was not considered to be benign in a person with my family history. Therefore, I was put on a beta blocker called Toprol XL (metoprolol succinate), to slow my heart down. The HCM cardiologist told me what I had been previously told about my heart "chambers expanding more when exertion stopped", was only that cardiologist's "guess," and it was not true. He told me my heart was stiff and that is what causes the SOB upon exertion, and that stiffness is definitely one of the problems in HCM. After two years under his care, I learned about programs called HCM COE. (Hypertrophic Cardiomyopathy Center of Excellence), which meet a standard of delivery of care with criteria set forth by the HCMA. I decided to go to a high-volume COE for an evaluation. I had an exercise echo there, which was very comprehensive, unlike the only other one I had had in 2010. Then I saw the head cardiologist at the COE. After evaluating my records and test results, he formally diagnosed me with Hypertrophic Cardiomyopathy and NYHA Class 3 Heart Failure. He immediately referred me for an ICD due to my risk factors for SCD. I permanently switched my cardiac care to the HCM COE. The COE electrophysiologist recommended an S-ICD (subcutaneous) with no leads in the heart. My insurance, Anthem, bucked that recommendation. She did a peer to peer review and they still bucked it. She was flabbergasted that they were denying a COE's recommendation. To

compare, Mayo Clinic is also a COE, so this is the level of expertise we are dealing with. The fight with my insurance company, Anthem, lasted for two months, leaving me at risk for a SCD during that time, due to their red tape. When it was all said and done, they agreed to pay for a regular ICD, the kind with leads in the heart. This is what I had implanted in April of 2019 because I could not afford to pay cash for the recommended S-ICD. Now I have concerns regarding having wires in my heart. One of my cousins had one of her leads come loose and it was "flopping" around inside her heart chamber giving her small shocks. I have another cousin who had a lead fracture and it, of course, required replacement which is a very delicate and potentially dangerous surgery. More things on my mind daily. I already pay a higher premium to have a higher level of insurance benefits, and I do this solely because of my cardiac condition. Currently, I am paying over \$9000 annually out of my pocket for medical insurance premiums to have the higher level of benefits in an employer sponsored medical insurance plan. I continue to have to pay co-pay and a deductible as well. The premiums are burdensome financially, but necessary to protect personal finances from easily getting consumed by a medical crisis. The exercise echo that I am required to have annually is billed at over \$8000 alone! My ICD has to be monitored and interrogated on an on-going basis as well, which is expensive. My medical insurance policy was a great disappointment to me again this year when I had two gaps of getting the beta blocker due to appeals with my insurance company. The first issue was because the insurance company changed the formulary IN THE MIDDLE OF A BENEFIT YEAR! I tried taking the generic version of the beta blocker and had a lot of break-through arrhythmias. I've tried using the generic more than once and it is always the same issue. My HCM COE cardiologist told me that due to this, I should only take the brand name product (Toprol XL), and that is what my insurance company was denying as they didn't want to pay for a brand name. This is a drug that was approved by the FDA in 1992!! Due to the gap in being able to get the medication covered during the appeals process (and knowing it took two months for the ICD approval with more than one appeal in the process), I paid cash for Toprol XL with a prescription submitted by my cardiologist to a pharmacy in Canada. It was more affordable than prices in the USA. Now I have learned that this "red-tape process" is required once a year with my insurance company before they will pay for the Toprol XL, and I wonder if I will be without my medication again, or have to pay cash for some while they go through their self-created hoops with my same medical information that is not going to change since this is a chronic disease. After experiencing this, it has been very alarming to me and constantly in the back of my mind regarding what is going to happen once Mavacamten, and other novel HCM drugs, go on-label? It is great that we have some hope with this novel drug, but will we be able to afford it? There are no drugs that are specific for the muscle cell issues caused by HCM, and this is our first hope for an actual treatment for the disease, instead of just managing the symptoms with drugs created for different diagnoses. After so much heart ache of losing family members, and knowing that I am gene positive and that I passed this along to my son, who is also gene positive, I just want that hope that I will be able to afford it for myself, and that it, along with hopefully more drugs will be available for my son (should or when he develops the disease) and for current and future generations of people suffering from HCM.

Due to my diagnosis, and watching my family and extended family's medical care, I now also pay an annual premium for Air-Vac insurance. I recently started looking into the "Fly Me Home" option with the Air-Vac company (requiring an additional premium, of course), as if I had a significant cardiac event, I would want to be treated at an HCM COE, and there are a limited number in the USA.

2017 was a very hard year. I lost three more cousins in my generation due to HCM. Thankfully all three of these had ICDs. The medical care is improving. One of them was 'end stage' and his ICD was turned off. The other two were alone when they died and both of them were just two years older than me. I know that an ICD will only fire a certain number of times in a row for an event. I always wonder what their deaths were like. I hope they were unconscious for the whole thing. My familial generation continues to shrink prematurely. When there is a new birth in the family, I wonder if that child was passed the tainted genes.

There have been emotional struggles, financial struggles, and physical struggles. As my HCM continues to progress, more and more issues arise that I have to deal with on a daily basis. There are always more and more things that compromise the quality of my life and it is in my face constantly that I am not normal. The only hope I have are these novel drugs on the horizon, or a transplant, which there is no guarantee that a person will be approved for a transplant, and one is typically required to be "end stage." I watched my sister navigate through that complicated process, and I currently have a cousin who is in the process (of trying to get approved). When I walk up an incline I now often have a hypotensive response. This was caught during my latest exercise echo, and now I know what that feeling is identified as when it happens. I cannot do much in a bent over position as I run out of air. My heart is too stiff to pump correctly in that position. That is not a situation of exertion like walking up a flight of stairs, or up a hill, or God-forbid, needing to run, but the simple position of just bending over equals SOB for me. Now also, lying down in bed and getting situated to prepare to sleep, that causes me to pant. Repositioning one's body in bed, that is something that the average person doesn't realize they take for granted, it makes me pant. It is really depressing writing my story, and I'm sure there are things I haven't even touched upon. I try very hard to live my life as an optimist, and it is difficult for me to write all of this negativity.

It is my hope that my story will help someone who is normal, to understand some of my struggles as a result of the familial HCM that has robbed so much from my family and myself. It is my hope that these novel drugs will be available and affordable as they get FDA approval, as it really seems to be our only hope. I think back to when I took my mom to the hospital to be cardioverted and they had left the door open and I watched her body 'jump' on the bed from the shock, it did not work, so they upped the joules and did it again. It was so surreal, like I was in a television show! Sad and helpless is how I felt for my mother. Now I feel like "I'm next." If there is going to be a drug approved that can specifically help this disease, but yet American citizens cannot access it due to it being unaffordable, that will be the biggest fail of the century for the USA. It may even cost me my life.

September 15, 2021

RE: Mavacamten for Hypertrophic Cardiomyopathy – Draft Evidence Report

Dear Dr. Pearson,

Bristol Myer Squibb (BMS) acknowledges the importance of fully and accurately understanding the value that innovative therapies provide to patients, and we appreciate the opportunity to respond to the Institute for Clinical and Economic Review's (ICER) draft evidence report, "Mavacamten for Hypertrophic Cardiomyopathy," posted on August 18, 2021.

Mavacamten was designed and developed to potentially fill a critical unmet need for patients with obstructive hypertrophic cardiomyopathy (HCM) by targeting the underlying cause of the disease. BMS is committed to a holistic, evidence-driven approach that incorporates patient preferences, total health system value, multi-stakeholder input, and the most up-to-date clinical evidence to determine a treatment's value. As we have stated from the outset, we are concerned that the ICER review is premature given the evolving body of scientific evidence for mavacamten. Furthermore, the ICER model, as detailed in the draft evidence report, is fundamentally flawed as a result of two major design decisions: comparing therapies to mavacamten in the absence of critical data required for a methodologically rigorous assessment and ignoring epidemiological evidence on mortality and disease progression in obstructive HCM. As a result, the ICER model provides an unreliable assessment of the net health benefit of mavacamten. We also found programming and reporting errors that—though perhaps not critical to final results—could undermine the credibility of this premature exercise.

Premature Assessments Preclude Key Long-Term Efficacy Data Impacting Accurate Evaluation

BMS understands the methodological challenges associated with conducting evaluations in the early stages of a product's lifecycle. Longer follow-up data should be used where possible. The data on mavacamten continue to evolve, and should mavacamten receive FDA approval, additional data will become publicly available through peer-reviewed publications. Currently, there are three ongoing clinical trials evaluating the long-term efficacy and safety of mavacamten in obstructive HCM: MAVA-LTE, which is the 5-year long-term extension study that includes patients from the Phase 3 EXPLORER-HCM trial¹; PIONEER-OLE, which is the open-label extension study of the Phase 2 PIONEER-HCM trial²; and VALOR-HCM, a Phase 3, placebo-controlled trial evaluating the use of mavacamten prior to septal reduction therapy (SRT), which includes myectomy and alcohol septal ablation, and will have a long-term extension dosing period.^{3,4} Interim results are available for MAVA-LTE (60-week data) and PIONEER-OLE (48-week data), while VALOR-HCM is expected to read out in 2022.^{1-3,5,6}

Briefly, in the interim analysis of MAVA-LTE, the EXPLORER-HCM cohort demonstrated durable improvement in symptoms, heart function, echo-imaging, and biomarkers.⁵ Similar results on the effectiveness of mavacamten were observed in the interim analysis of the PIONEER-OLE study. Results also showed that treatment with mavacamten was associated with a favorable reduction in the septal myocardial thickness with no accompanying changes to the myocardial thickness of the posterior wall and the left ventricular ejection fraction.⁶ The safety profile of mavacamten was generally comparable to that of placebo in the Phase 3 EXPLORER-HCM⁷ with no additional safety signals detected in the interim MAVA-LTE analyses.⁵

Inaccurate Assumptions on Mortality and Disease Progression

BMS further recognizes the inherent uncertainty associated with modeling in the absence of comparable data for the different treatments. Given the heterogeneity of obstructive HCM and the reservation of disopyramide and SRT as later-line treatments,^{8,9} the patient populations in real-world observational studies of disopyramide and SRT may be somewhat different from the intended and studied patient population for mavacamten. There are no comparable randomized data in obstructive HCM patient populations for disopyramide and SRT that can support a scientifically robust and credible evaluation versus mavacamten.

In addition to these modeling challenges associated with the rapidly evolving evidence for mavacamten and the lack of comparable randomized data for disopyramide and SRT, the current ICER model was predicated on several spurious clinical assumptions—most notably, on mortality and disease progression—that overlook widely understood and recognized clinical evidence relating to obstructive HCM and its patient population. In the ICER model, mortality risk does not increase with more severe disease (higher NYHA class). This assumption contradicts well documented findings in literature that mortality risk does increase with higher NYHA functional class in HCM and obstructive HCM.¹⁰⁻¹³ BMS-sponsored research with the Sarcomeric Human Cardiomyopathy Registry (SHaRe), which was recently presented at the Heart Failure Society of America Congress 2021, corroborates these findings.¹⁴

The ICER model also does not reflect the natural course of obstructive HCM, particularly in patients with symptoms refractory to first-line pharmacologic therapy (i.e., beta-blockers and calcium-channel blockers). Many of the patients (92%) in the EXPLORER-HCM trial were already on standard first-line pharmacologic therapy for obstructive HCM prior to enrolment in the trial⁷; for these patients, disease progression will likely continue if treated on standard first-line pharmacologic therapy alone. However, the ICER cost-effectiveness model assumes that after a few weeks of treatment, disease progression abruptly stops for all patients, including those on standard first-line therapy alone.

Programming and Reporting Errors

Lastly, besides the inaccurate clinical assumptions mentioned above, there were also notable programming or reporting errors related to the model, including but not limited to the following:

- Incorrect inputs:
 - The periprocedural mortality rates for SRT used by ICER (texts on p.109 of draft evidence report) were inconsistent with the Liebrechts 2015 study¹⁵ that ICER cited and with Table 3.8 of the draft evidence report.
 - The utility decrement with age should be 0.0007 per year (texts on p.111 of draft evidence report).
- Inexplicable results: Although total life years should equal the sum of years that patients spend in each of the NYHA classes, ICER reported for the SRT arm that patients spent more years in NYHA class I than their total life years (Table 4.3 of draft report).
- Sensitivity analyses that lack face validity: Because the ranking of health state utilities by NYHA functional class was not preserved in the sensitivity analyses, patients with greater symptom burden (higher NYHA functional class) could end up with better quality of life (higher health state utility) than patients with milder symptom burden.

In conclusion, we would like to reiterate our concern that this evaluation was premature and flawed given the evolving evidence for mavacamten and the lack of comparable randomized data in obstructive HCM patient populations for disopyramide and SRT. The model was further based on clinical assumptions—most notably regarding mortality and disease progression—that underestimate the disease burden and unmet need that patients with symptomatic obstructive HCM face and likely undermine the model's ability to accurately estimate treatment health benefits. There were also programming and reporting errors that affect the interpretability of the draft results. Correcting those errors will not, however, affect the fundamental flaws in the research design and draft model, which currently undermine its usefulness to payers, clinical decision-makers, and patients.

We would respectfully ask for ICER to consider our comments in the preparation of the final analysis and report and to take the time to construct a more robust and credible analysis.

Please let us know if you have any questions regarding our comments.

Sincerely,



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September 15, 2021

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Subject: Patient Perspective - Public Comments on Draft Evidence Report and Draft Voting Questions – Mavacamten

Dear Review Committee,

Thank you very much for giving us (the HOCM patients) the opportunity to provide comments on the review of the following documents:

1. “Draft Evidence Report for Mavacamten for Hypertrophic Cardiomyopathy: Effectiveness and Value” prepared for the California Technology Assessment Forum (CTAF) – August 18, 2021
2. “Mavacamten for Hypertrophic Cardiomyopathy – Draft Questions for Deliberation and Voting: October 22, 2021 Public Meeting”. As stated these questions are intended for deliberation between ICER and the CTAF voting body at the public meeting.

The deadline for sending our input is today (September 15, 2021) @ 5pm ET.

My comments to both documents are foremost from a Hypertrophic Obstructive Cardiomyopathy (HOCM) patient perspective. I was diagnosed 4 years ago with HOCM, when it manifested itself after a sudden uncontrollable asthma attack during an international business trip. Five months after my diagnosis due to my severe symptoms, and the fast progression of my HOCM disease, I had to retire early from my job. Secondly, I will review these documents from the perspective of a pharmaceutical industry professional with 25 years of experience in access, pricing, and reimbursement, and as a person who prepared documents for HTA reviews as well as worked on recommendations for final prices for multiple drugs and vaccines in the US and ex-US markets, as well as engaged in writing and implementing contracts with payors.

Even though I had very regular check-ups and diagnostic tests to eliminate any potential issues due to my multiple comorbid conditions, never ever have I demonstrated any symptoms related to HOCM before, and there never was a heart murmur prior to my diagnosis. After my major asthma attack on the business trip overseas, I had a comprehensive check-up with my pulmonary specialist and that’s the first time I manifested a very distinct heart murmur which led to multiple tests, diagnostic evaluations including cardiac MRI, that confirmed my HOCM diagnosis. I was diagnosed with NYHA Class III then and I am still at that class stage. I am not going to go into the other details of my disease, but I am sharing this much to highlight that how this disease manifests itself is very unique to each patient and the severity at diagnosis time varies from patient to patient. Not only my situation was puzzling and alarming to the experts who deal with

HCM and HOCM particularly, but the progression of the disease was also quite concerning to my healthcare providers. I was given strict medical orders as to what I can and cannot do, started on medication therapy which became a cocktail of medications, and into medical dose escalations to get a control of my disease and symptoms. As a person who never had to take beta blockers and calcium channel blockers before in her life, not only it was very difficult for me to initially handle the impact of these medications and the impact of the daily HOCM symptoms, it was quite difficult to describe to someone who has no idea what it does to the quality of life of a person who is experiencing this disease. It was puzzling and concerning to me and to my loved ones to see how suddenly I was out of breath, experiencing chest pain, and getting stuck at the stairs after just going up 2-3 steps. The blockage pain is very excruciating, and it feels like a sudden tear opened in my esophagus area and every breath I am trying to take leads to very sharp pains like my heart is being torn apart. It took a good 2 years to understand what triggered some of symptoms, the reasons behind syncopes, and still some symptoms are happening out of the blue. I am actively working with my healthcare providers who are experts in the designated Center of Excellence academic medical center. I daily collect blood pressure data, pulse, record what I eat and drink, including the quantity, and record any level of exercise for a regular daily routine of life. Please note, the term “exercise” is not how much time I spend at the gym, but daily housework, walking, basic chores, and simple garden work. When I go to the gym they are very structured using basic treadmill and bicycle as my body cannot handle anything else without causing dizziness, shortness of breath, and feeling faint. Given the way HOCM manifested itself in me, my current condition and treatments for managing my disease, definitely led me to make major life style changes which also had a huge impact on others in my family. I must confess there are still quite many unknowns related to my symptoms on my “bad days” and how much I can accomplish on my “good days”, and how I might encounter an unexpected debilitating symptom on my “average days”. There is no way I could have continued performing my job at the level I was performing had I not retired early. This had a major economic impact on my family and my life plans.

You might ask why these details. These details are actually essential in understanding what this disease is; what is a meaningful improvement if a new medication is going to be added to the treatment; and if the magnitude of improvement is meaningful enough to improve the quality of life of the patients. All these components are the “social and indirect costs” that must be taken into consideration when evaluating the “value and effectiveness of a new medicine” for this condition. ICER highlights these in Section 5, titled Contextual Considerations, and lists all the elements/attributes that must be considered in Table 5.1 when evaluating the “value and effectiveness of Mavacemten”. These contextual considerations make up the core theme in all of the questions that will be deliberated and voted on during the October 22, 2021 Public Meeting.

As a patient and as an informed expert on pricing and drug evaluations, what stuck out for me is the absence of any of these considerations in the models ICER created and evaluated. The conclusion at best is “promising but inconclusive”, however, a placeholder price tag is already provided, and the value of this medicine is going to be determined at the October 22nd meeting and voted on without any essential data. So my question to ICER is “Value of Medicine according to whom?”. What is the goal you want to achieve? Should patients who need this

drug be able to access it, afford it, and make sure they can take this “add-on” therapy as prescribed, be adherent and compliant and see improvements in their quality of life? If the evaluation has nothing to do with “value of the medicine” to the patients who need it, then value to whom is the big question. Is it the value to the pharmaceutical company or value to payers? I hope your final report clarifies all these questions.

After providing input in previous public comment times, and having reviewed all the documents provided by ICER, I feel it is important to highlight the major concerns I have regarding the models, and the data that is lacking to have a meaningful deliberation.

Major concerns that I have with the current economic models:

1. ***HOCM patients are the targeted population for this drug and the impact of any combination therapy is not considered:*** Mavacamten is an “**add-on medication**” targeted for **HOCM patients** as an add-on to existing standard of care (SOC) treatments (“usual care alone” as ICER defines) and “**does not replace**” any of the SOC treatments. There is no replacement to the existing costs due to the use of Mavacamten for a patient, in fact patients will realize additional drug costs. There is no data available to suggest that taking Mavacamten will reduce the number of medications a patient is taking, or eliminate the need for other medications during their treatment. Like myself, many patients are on cocktail of drugs. Combination therapy was not in the clinical trials and ICER has not taken that into consideration in any of their economic models.
2. ***ICER’s model is based on fixed NYHA classification and does not reflect the daily and lifelong variability HOCM patients experience:*** The variability in the manifestation of symptoms as well as the variability in the progression of the disease in HOCM patients are not considered in the model. The model held alive patients at a fixed NYHA classification. This assumption totally excludes the reality of fluctuations and neglects to capture the “value of stabilization” within the same NYHA class. This assumption is based on only 30 week experience with Mavacamten during the clinical trial.
3. ***Model assumes the clinical trial patients reflect the real-world population:*** ICER does not take into consideration the variability of patients’ ages, gender, race, and other comorbidities they might have in the real-world. The clinical trial had a controlled group and based on the exclusion criteria anyone with common comorbidities were excluded. There is a huge racial disparity in the clinical trial. The lack of age variability does not reflect the real-world makeup of HOCM patients.
4. ***Patient input from the survey conducted by ICER is not included in any of the model evaluations:*** Just like my own experiences, the report contains some of the information obtained from more than 600 patients. However, ICER did not include any of this input in the cost effectiveness or budget impact models. The social and indirect costs that impact a patient and their caregiver’s productivity, daily life and ultimately their economic wellbeing which impacts earning power and buying power has to be included

in the models. These are essential in determining the “value of the medicine”. All of these are the attributes that will determine who can afford Mavacemten.

5. **“Value of the Medicine”?** This question needs to be honestly and responsibly addressed. Putting a \$75,000 price point for the drug without taking any of the considerations listed above is concerning and definitely alarming. If we look at this from a pricing persons perspective, yes \$75,000 is a "great value" to the pharma company that is going to sell the product. At the same time \$75,000 price point is a "great value" to the PAYORS (or insurance companies) that are going to engage in "cost sharing schemes" with the patients by placing the drug into high tier placement in the formulary and restrict them further with step therapy and prior authorizations. In reality, the medicine to really show its true value needs to be accessible to the patients who need it, who can afford it so they stay adherent and compliant to the treatment protocols outlined by their healthcare providers. So the question becomes what needs to happen for a patient to afford this drug? How much can a typical patient afford to pay "copay" or "co-insurance" payment out of their "net income" on a monthly basis, while they still pay for their existing drugs and cover other living expenses. \$75,000 price point at a high tier placement could range from \$200-\$1000 copay per month or if it is a typical specialty tier placement with 25% of the manufacturer's price, this could at minimum lead to \$1562.50/month= $[(\$75,000 / 12) \times 0.25]$. This is just for mavacemten and it is paid out of Net Income. Per US Census Bureau the real median household income for the US in 2019 was \$68,703. This is gross income, not net income. US Labor Statistics breaks the median income down further as monthly income by age. . The monthly gross income by age is as follows:
 65+ years of age: \$4,297 per month
 55–64 years of age: \$4,910 per month
 45–54 years of age: \$4,927 per month
 35–44 years of age: \$4,862 per month
 25–34 years of age: \$4,032 per month
 20–24 years of age: \$2,750 per month
 Source: US Bureau of Labor Statistics

Based on this information, and if we assume all HOCM patients even make the Median Income, the simple question that needs to be answered is "what % of the patients who make the median income can afford mavacemten for their treatment?".

As a potential candidate for this medicine, a medicine that could potentially help with my symptoms and improve my quality of life, I am afraid I will be hard-pressed to be able to afford this medicine based on the current net income I have.

Response to Draft questions for Deliberation:

My general comment for the questions as I identified above is the following: THERE IS NO SUFFICIENT DATA FOR ANY OF THESE QUESTIONS TO BE ANSWERED.

Question 2 – How is the committee going to do a comparison when there is no data. Also disopyramide and its brand is not available. Due to the inconsistent availability it is not even in many of our treatment protocols..

Question 3 - This comparison cannot be done as there is no data.

Question 4-6 The report lacks any meaningful contextual considerations, therefore these questions are unanswerable at this time. Also what is “other” (as relevant) mean? What is the purpose of this item and how is it going to be deliberated on. “Other” is unknown and variable.

Questions 7-11 This whole section is dependent on Section 5. Which ICER clearly identifies as no data available. How can you measure, deliberate and vote on a group of questions where you have not provided any data. I am very disappointed to see these questions in the survey and be classified as the core items in decision making. In my opinion this is unethical and a clear indication of not understanding the disease.

Questions 12-14 – Long-term value for money

Same as above. With no head to head comparison to disopyrimide and other studies still underway regarding septal reduction therapy, as well as no data on contextual considerations, how can any thinking person be able to deliberate and vote on the unknowns to determine the “value of the medicine”.

In conclusion, I do not feel adequate data appears in the ICER report to achieve a meaningful patient centric opinion on the value of mavacamten. With so many unknowns, I cannot understand how a meaningful deliberation is going to take place and at the end what are the committee members going to vote on.

As a patient I am fearful that a novel drug that could have a positive impact on our treatment is not going to be accessible, affordable by any of the patients. In order to determine the “value of the drug” I would highly recommend that ICER and maybe BMS to conduct a real “willingness to pay” study with the patients to understand what their thresholds are. I would like to see science targeted to provide relief to patients be made available and affordable to patients.

Sincerely,

Ms. Billur T. Dowse

September 15, 2021

Institute for Clinical and Economic Review

Submitted electronically: publiccomments@icer.org

Dear Review Committee:

As a patient living with obstructive hypertrophic cardiomyopathy (HOCM), I appreciate this opportunity to provide public comment on the **Draft Evidence Report for Mavacamten for Hypertrophic Cardiomyopathy**. I am a 65-year-old, white woman, living in Annapolis, Maryland; my first symptoms were at birth. I was symptomatic as a child and teen (syncope, limited exercise) and officially diagnosed in 1988 (age 32) following a misdiagnosis of a myocardial infarction. Over the course of my life, I have received care from five private cardiologists, three academic cardiologists, five mental health professionals, and numerous primary care physicians in Kentucky, Minnesota, Virginia, Maryland, and Washington, DC. My comments include, by reference, my public comments made on April 29, 2021, on the Draft Scoping Document.

My comments are provided in three sections: 1) my personal health developments relevant to your review that have occurred since providing public comment on April 29, 2021; 2) general observations on the Draft Evidence Report; and 3) specific information regarding Section 5: Contextual Considerations and Potential Benefits and a plea that these factors be considered of high value by the appraisal committee upon voting on their inclusion.

Changes in my health since my last public comment to ICER

One of the resounding comments throughout the review of mavacamten has been the limitations of modeling that uses NYHA classification as a steady surrogate for HOCM patients' clinical course. This has been described as: "good days, bad days." To illustrate, I had an echocardiogram performed at a center of excellence yesterday and my LVOT gradient was 65 mmHg. This was >20 mmHg higher than the last performed in May 2020. During our discussion, neither the cardiologist nor I was surprised. I'm short of breath sometimes making my bed, walking less often, easily fatigued from the heat, and not sleeping well. He prescribed a change in medications (again), is helping to identify a mental health provider, and requested I go to Mayo Clinic for a 3-day evaluation for a septal myectomy in November (estimated \$2000 travel, lodging, co-pays, for the evaluation alone). In a few short months, in addition to these noticeable health changes, I've dropped one consulting client who required that I travel at the loss of \$4500/month income. I've attempted to exercise more indoors – Pilates costing \$185/month and a personal trainer who comes to my home at \$300/month.

Not once did we discuss the NYHA classification during my exam yesterday, in fact, I don't recall it ever being discussed by a treating clinician. This is primarily because he, like my prior cardiologist, understands the variability of my symptoms and relies more on *my personal experiences* to adjust treatment – e.g., whether how far I can walk, how much I'm sleeping, my emotional wellbeing, my desire to continue working, the familial support I need, and energy levels to have intimate relationships with my partner to name a few.

Briefly, the following are the LVOT gradients (in mmHg) at various times in my life.

1995	1996	1997	1998	2003	2006	2009	2011	2015	2018	2020	2021
57	22	30	87	55	83	71	74	38	44	43	65

Although not an economist (by a long shot) what keeps coming up for me is that there's nothing, except comparisons (admittedly limited) to one clinical trial, one drug, and two interventions that is *uniquely representative* of HOCM patients. A NYHA classification alone simply does not reflect the variability of this disease nor the immediacy in which many symptoms occur. In fact, I often felt I could substitute any number of other cardiac conditions (e.g., heart valve disease, atrial fibrillation) for the words – HOCM –and the findings and conclusions of would be the same. Nowhere is it evident that the unique lifelong challenges of living with HOCM were considered in the analysis.

General observations of the Draft Evidence Report

In addition to the above comments on the inappropriateness of squaring HOCM patients into a NYHA classification, I offer a few observations.

- Patients take a variety of medications at different dosages. Combination therapy is not considered and a model that doesn't include discontinuation of a medication is misleading. I have worked with HCM patients over four decades and don't recall one that hasn't changed medications numerous times.
- The most glaring omission from a patient perspective is the impact on emotional and mental wellbeing. This is a significant cost to patients in not only dollars and cents but also their ability to function as parents, employees, teachers, etc. which has a ripple effect on their families and society-at-large.
- There is no comment on the impact of gender, race or ethnicity in the review.
- Patient perspectives would have been more valuable if they had been categorized according to the therapy being compared rather than lumped together in one section. It would be more useful to know what patients' comments for drug therapies (i.e., disopyramide) versus septal reduction therapies.

Information regarding Section 5: Contextual Considerations and Potential Other Benefits and Disadvantages

Contextual Considerations ICER respectfully acknowledges that “. . . the burden of the disease can be very severe” and that “in addition to exertional symptoms and the risk of sudden death, patients face . . . “. Whatever comes after this is where the rubber meets the road.

At the risk of sounding as if I'm ranking the hardships of chronic health conditions, what makes HOCM so frightening and bone-chilling scary is knowing your heart could stop any minute. Period. Its not a disadvantage, discomfort, or disability, its death.

Arrhythmias, palpitations, and syncope can happen anywhere, anytime -- whether you're on an airplane (I've fainted inflight due to hypotension); in a Board meeting (I had to excuse myself due to palpitations and anxiety); underground on the subway (I laid on my back to prevent

fainting with palpitations that felt like a horse kicking the inside of my chest); while messing around in a hot tub (that put me in bed for the rest of the weekend); while scuba diving and stuck in a sunken ship (offshore during a vacation with no medical facilities within an hour's drive); while taking the bar exam (Holter monitor picked up 700+ PVCs within a 24-hour period) during sexual encounters (disgruntled younger woman being a smart-ass while wearing a Holter monitor); and while assisting in surgery to remove a brain dead young woman's heart for transplantation (when I was a transplant surgical PA for Emory University in the 1980s). The list goes on. These incidents were terrifying and sudden. They led to ambulance trips, ER visits, medication changes, wearing monitoring devices for weeks, mouth guards, additional pillows, shortened vacations, lost productivity at work, missed social interactions, broken relationships, changes in diet, and constant worry they would happen again.

The magnitude of the lifetime impact of HOCM is immeasurable. While ICER makes endless assumptions for its clinical and economic analyses, thousands of patients like me have experience, not assumptions, of the impact of this disease on our quality of life, our financial security, our relationships, and our perceptions of what it means to live the best life possible.

First, I was told in 1988 as a young woman "having children is risky," I lived with horrific fear of getting pregnant. Coupled with being told "you will have a shortened life expectancy" at the same time, I found relationships, courtship, and marriage off limits. I simply could not face my own illness, much less ask someone else to share the uncertainty of my future. If the doctors had no idea how long I would live, how could I plan for a future or expect someone else to take that risk? Likewise, mental health harm – anxiety, depression, mood disorders, irritability – has gone hand-in-hand with my HOCM since my diagnosis in 1988. Most of these appointments cost \$175 - \$275/hour and are paid out-of-pocket along with the costs of medications. For many years, mental health services were not a covered benefit by most health plans.

Regarding education and employment, I was tethered to jobs despite their interest or opportunities for advancement, simply to have health insurance and some semblance of a steady life. As I've shared before, I committed insurance fraud, falsified medical records, cancelled medical appointments, and lied on any questionnaire, "do you have heart disease" for most of my 20s, 30s, and 40s simply to keep a job with health insurance. At one point, while working as a consultant to the federal government, a colleague put me on his company's payroll at \$1/week simply to qualify for health insurance for the six months it took for the federal government to process my appointment. While I have been fortunate to have a good education and many rewarding jobs, it is apparent to me now that the potential loss of health insurance was the driving force behind the reasons, I chose the jobs I did, stayed in jobs longer than I wanted, and tolerated demotions or pay cuts.

Until the passage of the ACA, I was turned down for every form of health or life insurance possible. When unemployed during 2019, I paid \$900+/month for a state health exchange. I enrolled in long term health insurance at the age of 50 (15 years ago) during initial enrollment to avoid a physical exam, costing \$266/month (for 15 years; a total of \$47,800). Currently, I pay \$445 quarterly for Medicare Part A and B; \$136/month for Plan G on Supplement Part B; and

\$29/month for Part D, of which I am currently in the ‘donut hole’ for the remainder of the year. I pay \$500/month for counseling services.

One of the most palpable contextual considerations that impacts my quality of life is managing grief. Living with an incurable disease blurs one’s ability to feel free to live a life of adventure, promise, and joy. It thwarts your ability to see the glass ‘half full.’ I find that in my case, I experience three types of grief at the same time. I grieve the past, knowing I lacked the emotional stability I needed to explore adopting children or better relationships, or pursuing interests in writing and creative ventures because I had to have a job with health insurance. I grieve currently, for example, during the frightening COVID pandemic and being at high risk, isolation, living alone without access to caregivers should I become ill. And I have anticipatory grief, knowing I am living much longer than anyone predicted yet not knowing how I will age-in-place, or if my future includes hospitalization, surgery, or relocation to live near a center of excellence.

My quality of life is often hindered, like other HOCM patients, from feeling misunderstood. “You don’t look like a patient,” is heard all the time. In my 30s, working in Washington, DC, I sat for 45 minutes in my cardiologist office waiting for my appointment, only to be told when I confronted the intake nurse on the reason for the delay, “Oh, my gawd, I thought you were the drug rep. You certainly don’t look like a patient.”

Once when feeling too weak to stand at work, I called my cardiologist while lying on the floor of my office in a 4000-person federal office building. When they arrived, the EMTs crouched on the floor and unbuttoned my blouse to listen to my chest, all while my co-workers stood and gawked. They wheeled me down the long corridors to the elevators to take me to the hospital on a stretcher. I was so embarrassed and scared; I covered my face with the white sheet. “I think she’s dead,” I could hear the onlookers say in the hallway. “But she’s so young,” another would add. It was weeks before I had the courage to return to work; I was 35.

Like other patients, I have experienced an alarming lack of information by health providers about HCM, especially EMTs and ER personnel. While this is changing with increased education and awareness, more times than not, I have had to be the patient, patient advocate, crisis coordinator, and care provider at the same time – not a comforting feeling when you’re in atrial fibrillation at 150 bpm. During an exceptionally stressful holiday time in December 2006, I was admitted to George Washington Hospital ER than their observation unit for 24 hours. Every chemistry test imaginable was performed; imaging, review of symptoms, monitoring, etc. for PVCs and PACs so irregular the ER doctor said, “I have no idea what it is.” The adrenaline that coursed through my body was so palpable I could taste it. In the dark crying, all alone, I realized that not once had anyone asked me why I was alone in an ER with palpitations on Christmas Eve. Not once did anyone ask me if there was someone I wanted to call. I’m reminded of the powerful connection between the head and the heart every time I think of this story and the need for more understanding and awareness of the emotional toll HCM takes on patients.

As someone who suffers from an invisible disease, my inability to keep up on a group hike, stand in an exhibit hall for hours, or run to catch a flight poses awkward moments, especially with

strangers or those who are unaware of my illness. I make excuses a lot; I make up stories about having to “check my email first” or “wait to hear from my neighbor” or “need to get to the grocery” when asked to bike or hike on a day I’m not feeling well. I avoid any type of exercise that I believe will be problematic. One of my closest friends, a nurse, once said, “You act like this is something horrible when all it means is you have to take a few pills every day.” Her comment saddened me. In my efforts to appear ‘normal’, those around me are baffled how to help or what to say.

Potential Other Benefits or Disadvantages. As stated above, I have experienced extensive adjustments to my life due to HOCM. Being advised against having children was likely the thinking of the day; however, the pain and disappointment of not having children continues today, well after my ability biologically to have children. While I’ve not experienced a drug shortage, a beta-blocker (Betaxolol) I took for 20+ years was not always readily available. Both beta blockers and calcium channel blockers (my former treatments for 30 years) caused weight gain, insomnia, mood swings, and low libido.

In conclusion, I offer little to no suggestions on how to include this information objectively and fairly into your review but encourage you to do the best you can to see that it is. Like the Societal Perspective Input recognized in the *Evidence Report for Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease*, there must be ways to account for loss wages, productivity lost, mental health treatment costs, and school attendance in patients with various NYHA classifications (to which HOCM is being compared).

Throughout ICER’s website **patients** is either the first or second category of stakeholders for which ICER claims it is working, collaborating with, influence by, or wishes to hear more from. I hope this is the case and that patient information is, indeed, of critical importance. But, so far, I’m not convinced. The Draft Evidence review is chocked full of *assumptions* as to the clinical and economic impact of mavacamten and mountains of conclusions are made based on these assumptions. Yet, the question of whether to include patients’ **real world** experiences of living with HOCM and the potential benefit of the drug remain unsettled. To that end, much more can be done to reflect the unique direct and contextual considerations HOCM patients face throughout their life.

I respectfully urge the CTAF voting body to vote “5=very high priority” for questions 4-6 regarding the relative priority that should be given to any effective treatment for HOCM based on contextual considerations and to vote “5=major positive effect” on questions 7-11 regarding the effects of mavacamten on outcomes that inform judgement of the overall long-term value for money of mavacamten, with the understanding that the final determination of whether something is of ‘value’ or not, remains exclusively with the patient in consultation with their provider.

I appreciate the opportunity to comment on the Draft Evidence Report and look forward to further deliberations.

Sincerely,

Gwen Mayes, HOCM Patient



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 Hypertrophic Cardiomyopathy Association appreciates the opportunity to provide once again comment on the review of Mavacamten in hypertrophic obstructive cardiomyopathy (HOCM). We have outlined our significant concerns in the 10 points below. However, we feel it important to provide a preface to these points. The survey tool used by ICER to engage patients was poorly written and thereby failed to collect essential data about the real-world experience of patients. While our input was sought early in the process, much of what we suggested was ignored or not included. This has led to a report that fails to adequately capture many contextual factors that impact this patient population. Further, the failure to include any mention of "patients" in the agenda for October 22, 2021, public meeting clearly shows that the efforts to evaluate the economic impact of this new therapeutic option have nothing to do with the patients and everything to do with the payers. The entire ICER model lacks patient centrality.

We are concerned that ICER has not given adequate attention to the language in the 2020 AHA/ACC Hypertrophic Cardiomyopathy Guidelines with regards to high volume care models and shared decision making were largely ignored in the creation of ICER report.

1. **A model that relies upon a fixed NYHA classification does not reflect the lifelong experience of HOCM patients.** HOCM patients' symptoms vary considerably and do not progress in a predictable or linear manner. Patients unequivocally describe having "good days, bad days." The ICER long-term cost-effectiveness model held alive patients at a fixed NYHA classification which inadequately reflects the fluctuations of symptoms patients experience and minimizes the impact of such fluctuations. It also fails to value the benefits of stabilizing NYHA class and limiting the fluctuation of "good day, bad day," allowing a patient to live a more predictable life.
2. **The impact of combination therapy is not considered.** HOCM patients take a combination of drugs to treat symptoms such as arrhythmias, edema, palpitations, pulmonary hypertension, hypertension, atrial fibrillation, and congestive heart failure.

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Often additional drugs are taken to counter the side effects of primary medications. ICER does not address combination therapy in its review.

3. **Data from RCTs is known to over-state the health status of disease-specific populations.** ICER's review draws conclusions based upon data from one randomized clinical trial (RCT). It is well documented that RCT populations are generally much healthier than real-world disease-specific populations. There are always explicit and implicit exclusion criteria for recruitment into trial settings, including age, the existence of co-morbidities, and levels of healthcare access and utilization that make RCT populations rarely representative of real-world populations of need.
4. **Mortality among HCM patients may not be comparable to mortality rates of the US general population at similar ages.** The ICER review states, "mortality estimates were sourced from CDC and reflect US average mortality rates adjusted for age and gender as reflected by the overall averages of baseline characteristics of patients seen in the clinical trial . . . "Based upon data from one registry, mortality of HCM patients is approximately 3-fold that of the US general population; however, with proper treatment at high-volume centers, the HOCM mortality rate can approximate the mortality rate of the US population.
5. **Disparities in access to care were not considered.** Clinicians note that black HOCM patients appear to present with a different phenotypic profile than whites and are often misdiagnosed for extended periods of time. ICER did not include any accommodations for differences in race, ethnicity, or gender.
6. **ICER's cost-effectiveness model assumed a medication would not be discontinued.** Although 1000 simulations were performed with estimates across a patient's lifetime, no adjustments were made for discontinuation of mavacamten, standard therapy, or drug comparator (disopyramide). This belies common knowledge and experience in a lifetime condition. Further, it is reasonable that patients would discontinue medications or change medications as their disease progresses, side effects are deemed undesirable, or the cost of access to medication is altered and septal reduction therapies are desired.
7. **Relevant patient and caregiver information on the magnitude of living with HOCM was excluded.** Despite 600+ responses to a patient survey, individual patient and clinician interviews, several public comment periods, and inclusion of HCMA on the internal review, ICER did not include information from patients, caregivers, and other stakeholders of the potential for mavacamten to eliminate or reduce existing 'costs' of living with HCM and to society-at-large. Patients living with symptoms of chest pain, syncope, near syncope, palpitations, shortness of breath, brain fog, and fatigue are not present in all of life's activities include work, family,

and social aspects. Improvement in any symptom has tremendous value to patients, which this report does not adequately reflect. This includes patients' ability to manage and sustain treatment; achieve major life goals such as parenting, work, and education; remain financially secure; access care; and seek remedies for mental health conditions such as depression and anxiety. Additional analyses are needed to reflect the totality of the HCM patient's (and that of society, family, and caregivers) quality of life.

8. **More than direct care costs should be included in a cost-effectiveness analysis due to the lifetime burden of HCM.** Additional analysis is needed to include the "contextual considerations and potential other benefits" of patients and caregivers to more closely evaluate the overall judgments of the long-term value of mavacamten. While we had attempted many times to explain this to ICER during the many months of discussion, they failed to include the most important aspects of a patient's experience and economic burden.
9. **A budget impact conclusion is premature and could potentially discourage further innovation and/or access to care.** Stakeholders, such as health payers, have used budget impact analyses to justify access barriers for therapies despite the cost falling within ICER's recommended range. As the first-in-class therapy for an incurable, life-long health condition, any speculation of the budget impact of mavacamten is premature. Furthermore, patients should not be forced to have a more invasive therapy (e.g., septal reduction) because of the prohibitive cost of a medication that could manage their symptoms.
10. **Shared-decision making remains of utmost importance to HCM patients in all treatment decisions.** HCMA supports the 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy recommendation that shared-decision making between patient and provider is critical for treatment decisions. HCM is a lifetime condition, there is no cure. Treatment courses are highly variable and with patients at various times in their life with varied treatment goals to be expected. HCMA agrees with ICER's conclusion that ". . . preferences [in proceeding with septal reduction therapy] are so important that large variation will persist even with comparative effectiveness evidence" and that "decisions will need to be made on a case-by-case basis through discussion among patients, families, and clinicians.". Cost should not be a barrier to options.

Response to Draft questions for Deliberation:

Question 2 – You have not provided any useable information for any member of the committee to make a determination on the comparison between disopyrimide and Mavacamten.

Disopyramide is a generic drug, and there is no comparator study; therefore there is simply no data. Further, the limitations of disopyramide (generic) are that it is a multi-dose per day requirement that makes compliance very difficult for patients. The name brands option Norpace CR has been on and off for the past 8 years in the USA and is currently unavailable in the USA and Europe. Within the HCMA population, less than 10% of all HCM patients have used disopyrimide due to inconsistent availability.

Question 3 - How can the reviewer answer this question when the study is currently ongoing?

This comparison cannot be made as there is no data at this time. It seems disingenuous to even put this question on the list.

Question 4-6 The report lacks any meaningful contextual considerations, as we have noted time and again, therefore these are unanswerable questions.

#4 The options of "short-term risk of death OR progressions to permanent disability" make it clear to the HCMA that there is a complete lack of understanding of the disease process, its progression, or the daily impact of symptoms on the patient, family, or society. We encourage an added option for a reply of "Unknown" or "Inconclusive."

#5 How can the magnitude of the lifetime be questioned on a 38-week study – this question is unanswerable.

#6 What is "other" (as relevant)? What is the purpose of this item? It is not clear.

Questions 7-11

We are dumbfounded at the inclusion of the questions "patients ability to achieve major life goals related to education, work or family life," "Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life," "Patients' ability to manage and sustain treatment given the complexity of regimen," and "Society's goal of reducing health inequities" as these issues were not adequately addressed in the report. While HCMA believes the potential positive impact is worthy of the patients' access to mavacamten at a reasonable price, ICER has not included important information about the true burden of disease and, therefore, asks the review committee to vote on this no data is highly problematic. We question the ethical inclusion of these questions.

Questions 12-14 – Long-term value for money

Considering the lengthy list of contextual considerations omitted from this report, how can these questions be meaningfully asked of a voting body? With no head-to-head comparison to disopyramide and studies still underway regarding septal reduction therapy, these questions are left to be voted on by a committee that has no factual data to base any conclusion upon.

In conclusion, we feel that the statement "Following the public deliberation on this report, the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review." We do not feel

adequate data appears in the ICER report to achieve a meaningful patient-centric opinion on the value of mavacamten as they will lack the understanding of this complex disorder that has multiple pathways of disease expression, risks, symptoms, and currently no available therapeutic medications with a labeled indication for HCM.

There is a lack of data acknowledged repeatedly throughout the report. Yet, serious questions are being proposed to a voting body that cannot possibly have ample information to vote on matters potentially impacting patient care for decades.

While we appreciate the opportunity to comment on this critical matter to the HCM community, we are deeply concerned and disappointed in the lack of transparency to the actual burden of disease for HCM patients and families. We urge payers to review the final report from ICER with a cautious eye to the massive gaps in understanding the value of myosin inhibitors such as Mavacamten to the HCM community.

Sincerely,

Lisa Salberg

Lisa Salberg
CEO and Founder

September 14, 2021

To whom it may concern –

As you review Mavacamten for public consumption, it is my plea that you take into consideration the human side of the equation. My life with HCM (and my children's screenings) are difficult to quantify in a spreadsheet.

Mavacamten is a hope for the future. While BMS is currently seeking approval for the obstructed patients, it is not hard to believe that the non-obstructed will follow closely behind. My life has dramatically changed since becoming symptomatic and I hang on to hope this is a viable option to reduce my level of disability.

The issue with HCM is that my "disability" doesn't qualify as a disability in the states eyes. My shortness of breath, chest pain, inability to tie my shoes (on bad days) or work on my feet for 8 hours is in their eyes an inconvenience. For me living with HCM means yearly screenings at a hospital 3 hours from my home, requiring 2 days off work to schedule the required screenings, bloodwork, and consultation. It requires an overnight and meals in Rochester.

- It means I had to change jobs because I could not carry freight upstairs or lift boxes.
- It means I lost my health insurance
- It means we spend over \$10,000 a year on out pocket costs for screenings
- It means we spend over \$3000 a year on prescription co-pays
- It means lost wages and lost vacation time for bad days
- It means my life is dramatically altered by HCM

My hope for my children is that this and other first in class drugs for HCM are not price positioned such that they are indentured servants to their healthcare needs the way I am., Mavacamten would allow life to be much less variable. If this drug is priced such that they will be spending tens of thousands of dollars a year to be able to have the quality of life of "normal" person our family will be crippled for generations financially.

Health should not be a privilege that separates the ability of future generations from achieving middle class success. The cost basis of this drug is something that you can chart on a spreadsheet, my hope for the future and my family's future rests in one of those cells.

As you review the cost of this medicine, before you enter in a formula, I would ask you think about how it could impact multiple generations within a family and provide a new lease on life for those who have suffered the fate of both physical, mental and financial insecurity with HCM.

Regards,

Ross W. Hadley

September 15, 2021

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108
Submitted Electronically: publiccomments@icer-review.org

Dear Dr. Pearson:

Thank you for the opportunity to comment on the draft review report, “Mavacamten for Hypertrophic Cardiomyopathy: Effectiveness and Value,” dated August 18, 2021.

We appreciate ICER’s willingness to review comments and recommendations from the National Forum’s Value & Access Collaboration which works on these issues. The undersigned Value & Access Collaboration members, including patient, provider, payer, and public health organizations, jointly offer the following feedback for ICER’s consideration in the development of the revised review report.

In conducting a cost-effectiveness analysis of mavacamten, ICER has taken on a large challenge given the lack of clinical, epidemiological, and cost data and uncertainty around it.

We were gratified that several of our recommendations for the scoping document were included in the draft report.

We respectfully offer the following recommendations:

Inputs

While we appreciate the inclusion in the narrative report of patient perspectives and results from the patient survey because patient experience bears on outcomes, we recommend that this information be included in the economic model dataset. Otherwise, patient perspectives may not be considered by payers that will use the economic model dataset when making coverage decisions.

ICER assumed static levels of four inputs which impact the model’s utility:

1) Disease Progression

- ICER’s model reflected the stoppage of disease progression after the initial few weeks of treatment.
 - This is inconsistent with Sarcomeric Human Cardiomyopathy Registry (SHaRe) data showing that the cumulative burden of HCM is substantial and dominated by

heart failure and atrial fibrillation occurring many years after diagnosis. Young age at diagnosis and the presence of a sarcomere mutation are powerful predictors of adverse outcomes. The findings highlight the need for close surveillance throughout life and to develop disease-modifying therapies.¹

- According to the 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy (HCM), among referral-based cohorts of patients with HCM, 30% to 40% will experience adverse events, including: 1) sudden death events; 2) progressive limiting symptoms because of LVOTO (left ventricular outflow tract obstruction) or diastolic dysfunction; 3) HF (Heart Failure) symptoms associated with systolic dysfunction; and 4) AF (Atrial Fibrillation) with risk of thromboembolic stroke.²
- We suggest that this data be reflected in the model.

2) Mortality Rates

- ICER shows “mortality estimates were sourced from the CDC and reflect US average mortality rates adjusted for age and gender as reflected by the overall averages of baseline characteristics of patients seen in the clinical trial. Based on conversations with clinical experts and available evidence, mortality was assumed to be constant across NYHA class” (pg. 110). We would like to point out that:
 - SHaRe data shows the mortality of patients with HCM to be ≈ 3 -fold higher than for the US general population at similar ages.³
 - Studies conducted at centers of excellence consistently demonstrate mortality negligibly different from that of the general population.⁴
 - Thus, we recommend that the quality of care provided and the level of clinical expertise available be given more consideration in ICER’s analysis.

3) NYHA Class (pg. 22)

- The model held the proportion of alive patients in each NYHA class constant up to cycle 8. However, the disease course of HCM is not linear. Therefore, the model should reflect actual variance.
- There can be significant variability in a patient’s NYHA class from one day to the next. This variability, together with the subjectivity of NYHA class determination, limits the validity of this metric to gauge therapeutic benefit.

4) Discontinuation of Therapy (pg. 22)

- Discontinuation was not included in the model. This is inconsistent with real-world experience. Data shows approximately one in five new prescriptions are never filled; of those filled, approximately 50% are taken incorrectly, particularly with regard to timing, dosage, frequency, and duration.⁵ This should be accounted for in the model.

5.) Admission for Titration

- ICER refers to “other than an initial hospitalization associated with disopyramide” (see Table E10 – pg. 117). However, we do not see disopyramide listed in table E10.

Therefore, it is not clear whether the economic models assume hospitalization for titration of disopyramide or mavacamten. Studies have indicated that hospitalization for titration of disopyramide can be safely avoided.⁶ This would have a major impact on cost-effectiveness results.

Comparators

Because the only mortality effect across treatments in the model was associated with perioperative mortality from myectomy and septal ablation and no other adverse effects, the benefit of these treatments compared to mavacamten is overestimated.

The draft evidence report ignores the fact that the 2020 ACC/AHA HCM Guidelines recommend that strong consideration be given to referral of patients with obstructive HCM, who are candidates for invasive SRTs, to established high-volume-primary or comprehensive HCM centers to perform procedures with optimal safety and benefits outcomes. This information should be reflected in the model.

Because the model was stopped at 32 weeks, the progression for longer term financial benefits could not be calculated. Thus, long term benefits are potentially underestimated as recent data shows results from treatment with mavacamten at 60 weeks are consistent with the parent study, EXPLORER-HCM.⁷

However, we note concern with serious event occurrences in the EXPLORER-HCM trial.⁸ For example, the 6% of patients whose ejection fractions (LVEF) dropped below 50% would have to discontinue use of mavacamten, be followed more intensely, and require follow-up medical treatment. Thus, we recommend the model reflect harms which would impact both patient quality of life and cost.

Contextual Considerations and Potential Benefits

While ICER acknowledges lack of information from patients and caregivers of the potential benefits and limitations of the analyses in this report, these considerations are critical and impact patient care and decisions about treatment options and judgements of overall long-term value for money. The 2020 ACC/AHA Guidelines on HCM recommends (Class 1, Strong, B-NR) shared decision-making in developing a plan of care, including but not limited to decisions regarding genetic evaluation, activity, lifestyle, and therapy choices...” Accordingly, the Value & Access Collaboration recommends the contextual considerations that appear in [voting questions](#) 7-9 also appear in voting questions 1-4.

Cost-Effectiveness Analysis

We urge a degree of reconceptualization of the cost-effectiveness analysis. Given the variability of HCM and no specific scale for HCM patient assessment available, ICER needs to give more

attention to contextual data and patient perspective. In addition to NYHA class, we recommend ICER use the Kansas City Cardiomyopathy Questionnaire and research on patient perspectives in its analysis.

It is important to ask what society is “buying” with a new drug. Clinical indicators are, of course, critical, but from the patient perspective, what is being bought is at least twofold: symptom relief and worry relief. We note that in the draft report, per the online patient questionnaire, only 50.4% of patients felt that their treatment “worked well.” The remainder found varying degrees of problems. Only 43% reported no side effects (pg. 46).

These figures indicate that there is an unmet need for improved therapies. In particular, the report notes that there is an unmet need for relief of exertional symptoms for patients who do not have access to specialized centers.

It would also be useful to distinguish the QALY impact of:

- (1) clinical and symptom improvement;
- (2) clinical improvements without apparent symptom improvement;
- (3) symptom improvement without clinical improvement, and;
- (4) clinical improvement without symptom improvement.

In the draft report, ICER states that it continues to work on obtaining data to allow for a modified societal perspective to be presented in the revised Evidence Report. We strongly encourage ICER to pursue its goal to perform the analysis from the societal perspective as this could capture and monetize significant contextual considerations.

Potential Budget Impact Analysis

- We recommend that the report include clinical effectiveness and cost effectiveness, and not budget impact. Some stakeholders have used budget impact analyses to justify access barriers for therapies whose cost is within ICER’s recommended range. Payers can conduct their own budget analyses.
- The danger of projecting budgetary impact based on non-real world pricing assumptions and non-real world utilization rates is that it can trigger barriers to access to potentially cost-effective therapies. This has happened following release of other ICER reports.
- The risk of linking budget impact to recommended price ranges is that it could disincentivize innovation.

Access Considerations

As mentioned in ICER’s report, access challenges remain for patients to obtain care at centers of excellence.

Study findings suggest inequities in clinical care provisions for HCM exist based on race and gender. Black patients with HCM experience inequities in care with lower use of invasive septal

reduction therapy and genetic testing compared with White patients. In addition, women with HCM are under-diagnosed and referred to centers later than men, often with more advanced heart failure.^{9, 10}

ICER's analysis appears to assume that patients have access to the full range of treatment options and high-quality care. A considerable portion of the population does not have access to centers of excellence. This limits both options and quality of care. We believe that geographic availability of therapies and care should be factored into the model as well.

Determination of appropriate intervention for individual patients should be made by the patient and their physician. Mavacamten could offer an alternative for patients who do not respond to first-line therapy, or who are ineligible or high-risk for invasive therapy, or who do not have access to centers of excellence.

Again, thank you for your consideration. We look forward to reviewing and providing additional comments throughout the review process.

Sincerely,

Members of the Value & Access Collaboration representing the following organizations:

National Forum for Heart Disease & Stroke Prevention (convener)
American Association of Heart Failure Nurses
American College of Cardiology
American Heart Association
American Pharmacists Association Foundation
American Society for Preventive Cardiology
Association of Black Cardiologists
Association of State and Territorial Health Officials
BallengeRx Consulting
Global Healthy Living Foundation
Hypertrophic Cardiomyopathy Association
Independent Health
Institute for Patient Access
Mended Hearts
National Alliance of Healthcare Purchaser Coalitions
Partnership to Advance Cardiovascular Health
Partnership to Improve Patient Care
Preventive Cardiovascular Nurses Association
University of Michigan Center for Value-Based Insurance Design
WomenHeart

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Dr S D Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
BOSTON MA 02109

12 September 2021

PUBLIC COMMENT FOR REVIEW OF MAVACAMTEN FOR HYPERTROPHIC CARDIOMYOPATHY: EFFECTIVENESS AND VALUE

I refer to your recently released Draft Evidence Report for Mavacamten for Hypertrophic Cardiomyopathy ¹.

As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment fails to meet the standards of normal science apart from failing the accepted standards for fundamental measurement ². That is, your reports lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. I presume, as you subcontract your modelling, that this denial of normal science and measurement theory is shared by Professor Walton and others at the Center for Pharmacoepidemiology and Pharmacoeconomic Research at the University of Illinois at Chicago, College of Pharmacy. They must be congratulated. The Mavacamten model is just the latest example of this failure.

The ICER/Illinois type imaginary models as has been well established, violate the fundamental axioms of measurement theory in confusing ordinal scales with interval and ratio scales. While you might view these reports and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. This is now widely recognized; to the detriment of ICER and its contracted model builders.

The QALY, as you have been informed on a number of occasions, is a mathematically impossible construct with a paper in *F1000Research* and a letter to *Value in Health* pointing this out ^{3 4}. As noted in the latter, we have now experienced 30 wasted years in health technology assessment, with ICER supporting and perpetuating this charade. The key point is that in the case of Mavacamten we have too little data to make even a reasoned, and scientifically valid, claim for pricing and budget impact. This should be put on hold until more data become available instead of rushing in to invent modelled claims. But yet ICER/Illinois proceed to invent evidence to support pricing and access claims with impossible incremental discounted QALYs and impossible cost-per-QALY thresholds.

When pointing out the deficiencies of the QALY you have a standard response, couched in a series of unsubstantiated assertions. I quote from your response to my criticisms in your lupus nephritis evidence report:

As we have expressed before we (and most health economists) are confident that changes in the EQ-5D (and other multiattribute utility instruments) do have ratio properties. The EQ-5D value sets are based on time trade-off assessments (which are interval level), with preference weights assigned to different attributes. We fail to see why this should be considered an ordinal (ranked) scale. The dead state represents a natural zero point on a health related quality of life. Negative utility values on the EQ-5D scale represent states worse than dead. We do not find this lacks face validity⁵.

This is, with due deference, complete nonsense. If endorsed by the Illinois pharmacy group of expert imaginary model builders, this shows a woeful lack of understanding of measurement theory. You might have confidence that health economists share your unbounded belief that multiattribute scores have mystical ratio properties, but I can assure you that professional economists such as myself fail to share this vision (including Nobel laureates). We have been trained to respect the axioms of fundamental measurement and the standards of normal science; not imaginary constructs. There can be no doubt that multiattribute preference scores are only ordinal: this has been obvious (references can be supplied) for over 40 years. To be quite clear: ordinal scores cannot support claims for response as the distance between scores is unknown only the ordering of respondents (applying nonparametric statistics).

To create a QALY by application of a preference score to time spent in a disease state, you require a ratio scale. That is, to support multiplication, a true zero. Absent a true zero where the preference algorithm can create negative preferences, the ICER/Chicago QALY is a mathematically impossible construct. Perhaps, the Chicago expert group might care to comment on a recent US valuation of the EQ-5D-5L where some 20% of 3,125 health states yielded negative scores. Perhaps the Chicago experts might demonstrate how a ratio scale can have negative values. This is a contradiction of the established standards for levels of evidence; a proof would make a major contribution to measurement theory.

Your response is that this is a standard (although mathematically impossible) in health technology assessment.. People do many weird things yet we don't have to emulate them. Your defense that the belief in a ratio scale with negative values is shared clearly with the Illinois pharmacy expert group (and also with other academic expert groups you contract with). It is not a question of lacking face validity; it is a question of lacking construct validity. The multiattribute preference scores are dimensionally heterogeneous failing to meet standards of unidimensionality. Measurement must be in terms of single attributes. Perhaps your College of Pharmacy group might show us why this is not the case?

I think you misunderstand what ratio property means particularly as all direct and indirect preference instruments can produce negative responses or states worse than death. We have known this for at least 30 years and I would refer you to the classic paper by Patrick et al published in

1994 where he and colleagues considered preferences for health states worse than death for three direct preference instruments: category scaling (CS), time trade off (TTO) and standard gamble (SG) ⁶. Again, would your expert group care to comment?

The overarching criticism, however, is that the ICER/Illinois modelling and subsequent recommendations for pricing and patient uptake are entirely imaginary constructs. In short, the proposed ‘evidence’ you bring to the table to evaluate Mavacamten is invented through assumption driven lifetime simulations that fail the standards of normal science. Separating science from pseudoscience, as I assume the expert group is aware from the contributions of Popper and others over the last 100 years, is the questions of the credibility of claims, empirical evaluation and replication. As noted by a number of reviewers, the ICER model fails on all counts including criticisms of your approach that have been published over the past six years, notably in the University of Minnesota journal *Innovations in Pharmacy* ^{7 8}. Your claims are imaginary assumption driven simulations. Again, I would encourage the expert group to defend this belief and make clear why formulary decisions for pricing and patient access should be driven by non-credible, non-evaluable and non-replicable claims. Perhaps I might caution not to restrict a response to ‘everyone does it’. That is too easy and begs the question.

A further question is the potential multiplicity of models. Assumptions can change and claims can change; in this disease area there could in principle be an infinity of Mavacamten models created by an infinity of assumptions. How does your expert Chicago group assert that one model above another is the only relevant model for resource allocation and pricing decisions? It is important to know. Claims for the ‘realism’ of assumptions, based on past observations is not a defense, nor probabilistic expectations; Hume and Russell made this quite clear some three centuries and one century ago respectively. Why should anyone believe your modeling? Perhaps you could explain.

Let me consider some more specific issues with the imaginary assumption driven College of Pharmacy expert report. I have framed these in terms of questions where I would appreciate a response to each in respect of your draft evidence report (in addition to those raised above):

1. Is there any reason why BMS, formulary committees and insurers should take any account of your claims when, as the model is driven by assumption, there are any number of alternative models, each with probability sensitivity analysis, that could be constructed to give alternative imaginary claims?
2. Would you agree that your model fails the demarcation test between science and pseudoscience as the claims made are not credible, empirically evaluable nor replicable?
3. Is there a unique feature of your model in its choice of assumptions for model structure and inputs that sets it apart from all other possible models to support comparative claims for Mavacamten that may enhance its appeal to BMS, formulary committees and insurers?
4. Recently, ICER published a real-world evidence update for its final evidence report on prophylaxis for hereditary angioedema ⁹. How soon do you envisage revisiting the model assumptions for Mavacamten to provide possibly revised claims for pricing and access? In what time frame? You should make clear that any imaginary claim is provisional.

5. Will (and when) the Mavacamten model be posted to *ICERAnalytics* so that BMS, formulary committees and insurers can manipulate the various assumptions to create new and competing claims?
6. As you are aware, the consensus among those economists and others with an awareness of the axioms of fundamental measurement, is that the various direct and indirect multiattribute preference instrument produce only ordinal scores. However, in previous correspondence you have argued that these instruments actually produce ratio scores even though there is no true zero. Do you still subscribe to this belief? If so, why? Do you have a proof of this belief that the ordinal preference scores are actually ratio scales in disguise?
7. Although not stated explicitly (and the source is obscure) the assumption is that your utilities (technically correct term is preferences) are from the EQ-5D stable; probably the EQ-5D-3L. Although this can produce negative preference scores for the health states you make no mention of this and provide no information on the distribution of these scores? It would be useful to provide them although they are only ranked ordinal scores.
8. If, in future assumption driven claims, you propose the use the EQ-5D-5L to create QALYS (even though mathematically impossible) how to propose to consider the potential impact of this ordinal measure, where according to the latest US valuation, 20% of the 3,125 health states create negative scores? This raises the intriguing possibility of impossible negative QALYs! In addition, the creation of an aggregate utility (mathematically impossible: think medians) to populate your model will actually deflate the average utility and may even create a zero or negative score? Will you be providing a distribution of these scores?
9. Given the potential for assumption driven revisions to your imaginary models would you agree that any and all model claims should be treated as provisional and subject to change at any time?

Your standard defense of these criticisms is that your methodology is the one everyone else has pursued for the past 30 years in health technology assessments. This is hardly a defense, merely an excuse. Why persist in following a failed methodology? It would have been appropriate to inform BMS, and other companies that have ‘engaged’ with you on the QALY, which is central to your cost-per-QALY claims and thresholds is, as you have been informed on a number of occasions, mathematically impossible¹⁰. But yet you deny it.

Yours sincerely and in anticipation

Paul C. Langley, Ph.D.
Adjunct Professor
College of Pharmacy
University of Minnesota

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September 15, 2021

Dr. Steven D. Pearson
President
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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-to-day 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

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 (HCM) 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-morbidities¹⁰ 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 patients¹³ 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.

¹⁴https://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