Mavacamten for Hypertrophic Cardiomyopathy: Response to Public Comments on Draft Evidence Report

October 7, 2021

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Response to Comments from Individual Patients, Caregivers, and the Patient Community

We are deeply grateful to the patients with hypertrophic cardiomyopathy (HCM) who have submitted public comments. The comments are detailed and evocative, and they demonstrate the difficulties faced by patients with HCM. In addition to symptoms, they include detailed information about difficulties with work, relationships, and both access to care and difficulties interacting with health care systems.

The comments also contain detailed information about costs and the impact of high costs on patients. For example, one patient reports spending over $10,000 per year on out-of-pocket costs for tests and $3,000 on prescription copayments. Another patient said, "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 failure of the century…"

Overall, these public comments remind us of the tremendous burden of symptoms for patients living with HCM. But the comments also remind us of the mental anguish that comes with uncertainty, difficulties accessing care, and concerns about cost. This process has convinced us that there is substantial unmet clinical need for patients with HCM and significant need for improvements in systems of care, affordability, and access to expertise.

We are tremendously grateful to the patients who have enriched our report by sharing their stories.

#	Comment	Response/Integration
Manufacturer		
Bristol Myers Squibb		
1.	**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 trial; PIONEER-OLE, which is the open-label extension study of the Phase 2 PIONEER-HCM trial; 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. 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. Briefly, in the interim analysis of MAVA-LTE, the EXPLORER-HCM cohort demonstrated durable improvement in symptoms, heart function, echo-imaging, and biomarkers. 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. The safety profile of mavacamten was generally comparable to that of placebo in the Phase 3 EXPLORER-HCM with no additional safety signals detected in the interim MAVA-LTE analyses.	We appreciate (and agree with) your recognition of the difficulties with evaluating comparative effectiveness of therapies with limited follow-up data. We have followed these recent reports, including the conference presentations, with great interest and we have incorporated them into the report. We appreciate the diverse evidence base created by Bristol Myers Squibb and the trialists, including interesting and important economic and health status information. We structure comparative effectiveness questions around questions that are important to patients and caregivers making clinical decisions. Conversely, we would not choose questions simply because prior or conclusive evidence already exists. In this way, we are better able to highlight both existing evidence and gaps in evidence that are relevant to decisions that patients will face after mavacamten becomes available. We reference and discuss these interesting and important studies in the report.
2.	**Inaccurate Assumptions on Mortality and Disease Progression.** BMS further recognizes the inherent uncertainty associated with modelling 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 modelling challenges associated with the rapidly evolving evidence for mavacamten and the lack of comparable randomized data for disopyramide and SRT,	After conversations with clinical experts and reviewing the literature, we purposefully abstracted away from having mortality implications for the different treatments as, overall, the mortality rates of HOCM patients are generally similar to a healthy patient population. Further, we found no evidence of mortality effects across treatments other than the perioperative mortality rates that we used. We acknowledge that on average NYHA class is associated with mortality, but that does not necessarily mean that drugs that change NYHA class also change mortality and, as such, that is not in our base case. That said, as a response to this concern, we have added a scenario analysis that includes higher mortality rates for patients in class III/IV relative to I and II. We also fully acknowledge that the treatment effects are applied early in the model and then held fixed across time.

	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 trial[7]; 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.	We found no evidence of differences in progression across treatments. It is possible that the assumption we used either underestimates or overestimates the actual treatment effects, however, this assumption is applied consistently across the treatment arms and the primary focus of the analysis is to estimate incremental treatment effects in comparison to incremental costs.

3.	**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 Liebregts 2015 study[15] 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.
		We appreciate the close review of the model and have fixed all of the input errors identified here. We have also edited the report to ensure consistency with the model. With respect to the NYHA class I years versus overall life years, it occurred because life years were discounted but the NYHA I years were not, and we have fixed that. As for the utility issue in the sensitivity analyses, the purpose there is to allow variation across all the inputs in simulations to assess the overall variance in the outputs of the model. We acknowledge the fact that there may be simulations where the utility for NYHA class II is lower than for class III as each is being drawn from a distribution, but we do not see how that has any impact on assessing variance in the model generally. Further, on average across the simulations, the utilities will be consistent as on average they reflect the base case.

Patient/Patient Advocacy Groups		
Billur T. Dowse		
1.	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 Mavacamten." 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.	The purpose of ICER including potential other benefits and contextual considerations is specifically to capture things that may be difficult or impossible to model. These issues will be addressed and voted on at the public meeting as you note. ICER's goal is to have the price of new therapies align with their value to patients.
2.	Major concerns that I have with the current economic models: ***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.	All of the treatment arms in the model involve combinations of treatments. Standard first-line therapies are part of all the regimens. The details are described in the report and supplemental materials.

	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.	
3.	***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.	NYHA classes comprised the best available evidence-based mechanism for looking at relative treatment effects in terms of QALYs and costs. The purpose of the model is not to specifically characterize potential individual variability in patient events but rather to best project incremental QALYs and incremental costs for a population. That said, we do conduct sensitivity and scenario analyses to examine potential variability in the outputs of the model.
4.	***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.	There is insufficient evidence to model treatment effects on subgroups of patients. The model does take the average age and gender from EXPLORER, but it applies that to each of the arms consistently. Further, we conduct sensitivity analyses to assess potential variance in the estimates.
5.	***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 Mavacamten.	We agree that a formal societal perspective analysis would be of interest. However, we were not able to acquire the necessary data. The existing patient input questionnaire is not designed to allow for projecting societal costs across NYHA class and, as such, does not allow the model to incorporate a formal societal perspective. In response, however, we have included two additional scenario analyses that project hypothetical changes on employment for patients to explore potential changes from a societal perspective.
6.	***"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	The economic model takes a health system perspective and uses a placeholder cost for mavacamten. We are not attempting to put a price on the drug – the cost used is placeholder price based on analyst estimates. We acknowledge that what is viewed as a cost to patients and or the health system may be seen as compensation to drug companies. Having a placeholder price makes sensitivity analyses easier to perform and read.

	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) X 0.25} … 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 mavacamten for their treatment?"	
7.	**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.	We agree that there are important gaps in evidence that make decisions for patients and clinicians more difficult. However, we do think that the EXPLORER trial provides promising evidence about mavacamten versus beta blockers and calcium channel blockers alone (although important unresolved uncertainties also exist). We highlight these important gaps in evidence, and they are influential in the evidence ratings in Section 3.3.
8.	**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.	We agree that evidence to support the use of disopyramide is lacking. We also agree that a direct randomized comparison of disopyramide to mavacamten would provide helpful information. We highlight these problems in Section 3.2 (“Uncertainties and Controversies”). We also agree that the national shortages of long-acting disopyramide create substantial problems for disopyramide as a therapeutic option. We discuss this issue in the Executive Summary, Section 3.3, Section 5, and Report Supplement Section B (as it was cited in the patient input questionnaire).
9.	**Question 3 –** This comparison cannot be done as there is no data.	We agree that a randomized comparison of septal reduction procedures to mavacamten would be useful information and does not exist. We discuss this in the Executive Summary and Section 3.1. There are non-randomized data estimating effects of septal reduction procedures, but we agree that data from a randomized trial would be better. We also highlight the fact that the VALOR trial, as designed, will not provide an estimate of the treatment effect of mavacamten versus septal reduction procedures (given the way that the endpoint is constructed).
10.	**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.	Contextual considerations are discussed in Section 5 of the report and will be amplified by patients and clinical experts at the public meeting. The “other” option allows the panel to raise additional contextual considerations.

11.	**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.	These are issues that are typically hard to directly measure and so we ask our expert panels, informed by patients and clinical experts at the public meeting, to make informed judgments.
12.	**Questions 12-14 – Long-term value for money** Same as above. With no head-to-head comparison to disopyramide 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."	The price of mavacamten will be set by the manufacturer if/when the therapy is approved. If we do not have a good estimate of that price, we will not be taking these votes.
Gwendolyn Mayes, JD, MMSc, Founder and Chief Concept Officer, GwenCo Health		
1.	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 additional 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. … 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*	Though NYHA class is a relatively lumpy scale, it offers the best evidence-based means for projections of QALYs based on utilities from HOCM patients that are associated with each of the treatment arms. The model is not designed to delineate or capture variance across individuals' day to day. It is designed to provide evidence-based projections of relative treatment effects in terms of QALYs and costs for a population. Note also that in addition to the base case projections, we conducted sensitivity analyses and scenario analyses to assess potential variance in the projections of the model.

	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.	
2.	**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.	ICER has found that in trying to highlight the relative benefits of treatments, that abstracting from discontinuation in the modeling rather than focusing on sequencing is more useful because in sequences the individual effects of therapies relative to their costs are hard to see. Further data on the exact timing in sequencing across treatments is not available. This was a modeling choice to focus on incremental effects and costs of mavacamten relative to other interventions. Also note that all the arms in the model are combination therapies. Further, we agree with the importance of examining stratified results by gender, race, and ethnicity. We point out (Section 3.2, "Uncertainties and Controversies") that more than 90% of patients in EXPLORER were white, leaving questions about the representativeness of the study population. However, to further address your concern we have also added additional language to the "Subgroup Analyses and Heterogeneity" section addressing these important issues. Namely there is no detectable difference in treatment effect among men and women. Inclusion of patients of color in EXPLORER was low and race-stratified data are not presented.
3.	**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	We appreciate all this very helpful feedback and information. In response, we have now added these contextual considerations to the report. We think these changes have helped us articulate the patient perspective in the report and we are appreciative.

	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…	
4.	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… 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	Again, we appreciate this very thoughtful feedback and we have made edits to the contextual considerations section to reflect these themes. We also extensively address the difficulties for patients related to access to subspecialty expertise and the difficulties interacting with less specialized health care workers.

	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…	
5.	**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).	We were not able to acquire adequate data to include a formal societal perspective to the costs. As described above, existing survey data is not structured in a way that could be used in the model. In response, however, we have included two additional scenario analyses that project hypothetical changes on employment for patients to explore potential changes from a societal perspective.
6.	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.	ICER values input from all stakeholders, especially individuals affected directly by a condition and patient organizations. We strive to empower the patient community to fully participate in every stage of our work, because only with their engagement and partnership will we begin to move our health care system toward a future in which we have affordable access to the care they need at a price that also sustains innovation. Our research is rooted in an academically rigorous and transparent process, based on the principles of evidenced-based medicine. Part of that process is to look at the clinical trial and other data through the lens of understanding the lived experience and then making decisions about how to weigh that data in a way that helps drive decision making about which treatments may offer the best value for the health system. We acknowledge our work is constrained by the availability of evidence from the manufacturer's clinical program at the time of the assessment and have provisions to update our work as real-world or other significant evidence is generated in the future.

		In considering the lived experience of HCM, we relied on the extensive input of the patient community which contributed more than 400 personal testimonials through our open input form. These insights are reflected in the Patient Perspectives and Contextual Considerations of our report. Additionally, we will have patient experts throughout the Public Meeting to provide further perspective on the lived experience and the value of the new treatments. Thus, the Independent Voting Councils have further opportunity to consider the clinical and economic evidence considering patient perspectives. We believe our approach provides comprehensive opportunities for the patient community to contribute to ICER research. Our teams are committed to ensuring that patient communities are listened to, respected, and have a positive experience in working with us to support fair pricing and access to innovative medicines.
Lisa Salberg, CEO and Founder, Hypertrophic Cardiomyopathy Association		
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.	Please see above.
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. Often additional drugs are taken to counter the side effects of primary medications. ICER does not address combination therapy in its review.	As discussed above, the analysis looks at mavacamten in combination with other primary therapies. It was not assumed that mavacamten would increase use of other medications to counter mavacamten side effects as we had no evidence to suggest this.
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.	We agree and we appreciate you making this point about the differences between evidence from trials and evidence from observational data (real-world evidence). We have added text in the “Uncertainty and Controversies” Section 3.2 about the limitations of data from trials and how real-world evidence could be used in the future.
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	Based on clinical input and our review of the literature we are assuming mortality rates equal to the US population for all the treatment arms. Also, however, we are adding a scenario analysis that includes higher mortality rates for those in NYHA class III/IV.

	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.	There were no available data to distinguish treatment effects across 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.	ICER has found that in trying to highlight the relative benefits of treatments, that abstracting from discontinuation in the modeling rather than focusing on sequencing is more useful because in sequences the individual effects of therapies relative to their costs are hard to see. Further data on the exact timing in sequencing across treatments is not available. This was a modeling choice to focus on the incremental effects and costs of mavacamten relative to other interventions. Also note that all the arms in the model are combination therapies.
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, palpations, 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.	We wanted to include a formal societal perspective but were unable to acquire the necessary data. We would need a means for estimating average changes in societal costs across NYHA class. In response, however, we have included two additional scenario analyses that project hypothetical changes on employment for patients to explore potential changes from a societal perspective.
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.	The survey data are not structured in a way suitable for inclusion in the model. We wanted to include a societal perspective but were unable to acquire the necessary data—which would have to include a means for estimating changes in societal costs across NYHA class. In response, however, we have included two additional scenario analyses that project hypothetical changes on employment for patients to explore potential changes from a societal perspective.

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.	ICER analyzes the short-term potential budget impact of changes in health expenditures with the introduction of a new test, treatment, or delivery system process. The potential budget impact is an estimate of the projected cumulative resource expenditure across all elements of the health care system for a specific intervention in a specific population over a period of time. ICER uses a five-year timeframe for its potential budget impact analysis to capture important potential clinical benefits and cost offsets provided by newer care options. Potential budget impact models aim to quantify the net cost over a short period of time for all eligible patients to receive the new technology. The role of the potential budget impact analysis is not to suggest a cap on spending, but to signal to the health care system that special arrangements, such as lower prices, enhanced efforts to eliminate waste, or prioritizing treatment for the sickest, may be needed to ensure availability of the new drug without short-term adverse effects on patients and families seeking to pay for affordable health insurance.
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.	We agree both with HCMA and the ACC/AHA guidelines about the importance of shared-decision making. Of note, the importance of shared-decision making was critical in our decision not to issue an evidence rating for the comparison between mavacamten and septal reduction procedures.
11.	**Question 2 – You have not provided any useable information for any member of the committee to make a determination on the comparison between disopyramide 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 disopyramide due to inconsistent availability.	We agree that the evidence supporting the use of disopyramide is relatively weak. There are data to support the use of disopyramide and we have provided the most authoritative data we could find (Section 3.2) although we also extensively discuss the limitations of these data as well as the known side effects of disopyramide. Accordingly, we have highlighted both the weakness of the data ("Uncertainties and Controversies, Section 3.2). We have also highlighted the problems for patients caused by the shortage of long-acting disopyramide (Sections 3.3 and 5.2 and the Executive Summary).
12.	**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.	We do not think that VALOR-HCM will directly address the question of the comparative clinical effectiveness of septal reduction procedures versus mavacamten because of the way the endpoint is defined (discussed in Section 1). We do

		think the trial will provide some important information about the extent to which mavacamten reduces the need for septal reduction procedures for patients who would be otherwise eligible. We do believe that some patients will want to consider the direct comparison of procedures versus mavacamten, and we know of no ongoing trials that will address the question directly.
13.	**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.	Contextual considerations are unrelated to any particular treatment – they are about the disease and so the length of follow-up in a clinical trial has no bearing on this. These same questions are asked in each ICER review – some conditions like HOCM may have a high lifetime burden of illness but a relatively low short-term risk of death or progression to permanent disability. Other diseases like pancreatic cancer may have a low lifetime burden of illness but a high risk of death in the short run. Questions 4 and 5 get at these issues. Question 6 allows the public panel to add additional contextual considerations if they feel this is warranted.
14.	**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.	We believe that the report plus the testimony of patients and clinical experts at the meeting as well as estimates of the effects of these therapies will allow the panel to make informed votes.
15.	**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.	The price of mavacamten will be set by the manufacturer if/when the therapy is approved. If we do not have a good estimate of that price, we will not be taking these votes.
16.	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	We believe that the report plus the testimony of patients and clinical experts at the meeting as well as estimates of the effects of these therapies will allow the panel to make informed votes.

	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.	
Ross W. Hadley		
1.	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 state's 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	We appreciate all of these thoughtful points and appreciate your perspective. We have included information throughout addressing the potential use of mavacamten in patients with non-obstructive HCM, the difficulties with health insurance, the difficulties with access to specialized centers, and the concerns with costs throughout our report.

	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.	
National Forum for Heart Disease & Stroke Prevention, Value & Access Collaboration		

1.	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.
	  ○ 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.
		Across age, people may eventually start to change NYHA class, and in fact it may change upwards or downwards across time, but we did not have data on this and opted to consistently hold it frozen for all the treatments following the treatment effect. If we applied dynamics in NYHA across age, it would be the same for all treatments and it is unlikely to have a large impact on the relative changes in QALYs and costs across treatments. Also we account for pacemaker use in the surgical arms. Otherwise, we did not see evidence of substantial enough differences in adverse events across the treatment arms that would merit inclusion.

2.	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:	Based on our conversations with clinical experts and review of the literature, we felt the best assumption for the base case was to have mortality equal that of the general population. We have included a scenario analysis with higher mortality rates for those in NYHA class III/IV. While there is likely variation in quality of care and outcomes across regions, etc., the evidence of mortality on

	○ SHaRe data shows the mortality of patients with HCM to be ≈3-fold higher than for the US general population at similar ages. ○ Studies conducted at centers of excellence consistently demonstrate mortality negligibly different from that of the general population. Thus, we recommend that the quality of care provided and the level of clinical expertise available be given more consideration in ICER's analysis.	average for HOCM patients suggests it is close to the general population.
3.	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.	The use of NYHA classes in the model reflects that they offer the best evidence-based mechanism for looking at relative treatment effects in terms of QALYs on average as well as costs. The purpose of the model is not to specifically characterize individual variability in patient events. That said, we do conduct sensitivity and scenario analyses to examine potential variability in the outputs of the model.
4.	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. This should be accounted for in the model.	ICER has found that in trying to highlight the relative benefits of treatments, that abstracting from discontinuation in the modeling rather than focusing on sequencing is more useful because in sequences the individual effects of therapies relative to their costs are hard to see. Further, data on the exact timing in sequencing across treatments is not available. Overall, this was a modeling choice to focus on the incremental effects and costs of mavacamten relative to other interventions. Also note that all the arms in the model are combination therapies.
5.	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. This would have a major impact on cost-effectiveness results.	Thank you for this important question. We have assumed that disopyramide would require inpatient admission for initiation. Although we are aware of the data from Toronto General Hospital (Adler 2017) demonstrating relative safety of initiation in the outpatient setting, we also note that in the US, both the FDA label and previous and prior ACC/AHA guidelines support initiation of disopyramide in the hospital (Gersch 2011). More recent guidelines simply state that "The US Food and Drug Administration-mandated safety precautions should be adopted when prescribing antiarrhythmic drugs" (Ommen 2020).
6.	**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	We included the use of pacemakers in the model. We have now included a scenario analysis that considers higher mortality rates for patients in NYHA class III/IV. Also, the model is not stopped after 32 weeks in the mavacamten plus standard first-line therapy or the first line therapy alone, rather there are no changes in the relative proportion of patients across NYHA class I, II, and III/IV other than through mortality. Hence the treatment effect lasts a lifetime for all the treatments. The model consistently assumes non-discontinuation for all treatment arms. Certainly some patients will switch

	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. However, we note concern with serious event occurrences in the EXPLORER-HCM trial. 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.	treatments and or sequency into surgical options. However, adding sequencing to the model would not be informed by data and would be less clear in delineating the relative average changes in costs and QALYs across the treatment arms.
7.	**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.	We agree with the importance of these issues. Questions 7-9 are meant to allow the voting panel to express the importance of these issues for the value of mavacamten generally.
8.	**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.	The use of NYHA classes in the model was chosen because they offer the best evidence-based mechanism for looking at relative treatment effects in terms of QALYs on average as well as costs. The KCCQ does not have the requisite evidence-based links to QALYs and costs as well as to treatment effects across the comparators. Also, it is not possible given available data to distinguish QALY gains into the categories suggested although that would be an interesting undertaking. We also wanted to include a societal perspective but were unable to acquire the necessary data, which would have to include a means for estimating changes in societal costs across NYHA class. In response, however, we have included two additional scenario analyses that project hypothetical changes on employment for patients to explore potential changes from a societal perspective.

	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.	
9.	**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.	ICER analyzes the short-term potential budget impact of changes in health expenditures with the introduction of a new test, treatment, or delivery system process. The potential budget impact is an estimate of the projected cumulative resource expenditure across all elements of the health care system for a specific intervention in a specific population over a period of time. ICER uses a five-year timeframe for its potential budget impact analysis to capture important potential clinical benefits and cost offsets provided by newer care options. Potential budget impact models aim to quantify the net cost over a short period of time for all eligible patients to receive the new technology. The role of the potential budget impact analysis is not to suggest a cap on spending, but to signal to the health care system that special arrangements, such as lower prices, enhanced efforts to eliminate waste, or prioritizing treatment for the sickest, may be needed to ensure availability of the new drug without short-term adverse effects on patients and families seeking to pay for affordable health insurance.
10.	**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. 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	We appreciate this important feedback. In our discussion of centers of excellence, we have now integrated these important citations you have provided.

	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.	
Anonymous, Patient with HCM		
1.	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…. 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.	We appreciate your thoughtful comments and perspective. We have included information throughout the report addressing the difficulties with health insurance and access to specialized centers, unemployment and under-employment, and the concerns with costs.
Other		
Paul Langley, PhD, University of Minnesota		
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. 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.	Thank you for your comment.
2.	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. 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	We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 in the report for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment. Specifically, many of the issues your raise are part of the "Other Benefits and Contextual Considerations" section, which are essential in assessing value.

	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 validity.* 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 you 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). 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*. 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.	

Tony Coelho, Chairman, Partnership to Improve Patient Care		
3.	**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.	We recognize that for newly approved treatments there is often limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost effectiveness, but we also believe that since these medicines will likely be soon available for use by patients, clinicians and payers, reliable information is needed now. This report uses data that is currently available and highlights the limitations of this data as well as the qualitative input of a range of stakeholders.
4.	**ICER chose not to incorporate key outcomes requested by patients and clinicians in constructing its model.** For many with HCM, the burden of disease can be severe. In addition to the risk of sudden cardiac death for most HCM patients, many patients also develop *exertional* symptoms limiting day-today functioning. 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). 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. Despite this perspective from patients and clinicians, the ICER model is driven solely by transition between NYHA classification categories.	The utilities associated with the NYHA classes in the model comes from EQ-5D surveys given to HOCM patients in those NYHA classes. NYHA class offers the best evidence-based way to calculate the average differences in QALYs and costs across treatments. We recognize there will be patient variability across time within any of these classes but as an estimate of average utility in any one time period for each of the treatments it was the best available option. The primary purpose of the model is to estimate the average gain in QALYs for a group of patients as well as the average costs rather than to predict or describe all potential heterogeneity across patients and time. That said, the model also includes various sensitivity analyses and scenario analyses to help assess potential variance in the model projections.
5.	**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	Please see above. The NYHA class was the best available option to consistently project costs and QALYs across the treatment arms.

	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.	
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. 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. In addition, utilities in RCTs tend to be inflated compared to non-RCT samples of patients 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.	We will add language acknowledging this limitation. However, the utilities from the trial have the distinct advantage that they reflect HOCM patients in the respective NYHA classes. This information is otherwise not available in the literature. Further, we conduct sensitivity analyses to characterize potential variance associated with the utilities and other variables. However, changes in the utility scores in the model do not have the effect of making mavacamten cost-saving at the reference price.
7.	**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	The model freezes the treatment effect at week 32 in the sense that the relative proportion of patients in each NYHA class stays the same other than incorporating mortality. Because of this the treatment effect in the model in fact lasts a lifetime.

	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.	
8.	**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, like HCM. We 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.	We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 in the report for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment. Specifically, many of the issues your raise are part of the "Other Benefits and Contextual Considerations" section, which are essential in assessing value.