INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Modulator Treatments for Cystic Fibrosis
Response to Public Comments on Draft Evidence Report

April 27

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

Dear Stakeholders,

ICER thanks each patient, caregiver, and family member who submitted public comments on our draft report on CF modulator therapies. While we are unable to respond to every letter, we would like to acknowledge and reflect upon several key themes we heard.

Many of you shared personal stories about how CF affects all aspects of your lives. Patients and caregivers described how CF robs them being able to spend time with family and friends, pursue educational/professional opportunities, and to plan for the future. Patients also shared how much Trikafta, Symdeko, Orkambi, and Kalydeco have helped them be more active, spend more time with family and friends, and plan for the future in a way that would have been unthinkable just a few years ago. We deeply appreciate the thought and effort that went into these comments, and we have described these important considerations in Chapter 2 of our report.

In our report Trikafta earned an "A," ICER's highest and rarest rating for comparative clinical effectiveness, indicating that we have high certainty that the treatment delivers substantial health benefits. Even though our report's findings suggest that the price of Trikafta is set too high in relation to its clinical benefits, we certainly do not call for non-coverage as the answer. We also feel confident that no insurer in the United States will even briefly entertain the option of non-covering Trikafta.

The experience with our last report may serve as a reassurance. To our knowledge no insurer, including New York Medicaid, who used our report as part of their identification of a price target for negotiation over the price of Orkambi, even whispered about possible non-coverage. In fact, New York Medicaid made explicit that in no way would its negotiation include any possibility of erecting increased barriers to access in any way. We too, at our public meeting, started by asserting that payers will cover these drugs (see video, 20:00-21:00).

When treatments are priced too high, they contribute to higher insurance premiums, copayments and restrictions on access. Studies have shown that as insurance costs increase patients may delay care, forego care entirely, or even drop their health insurance. This leads to increased suffering and mortality. We heard stories of CF patients in these exact circumstances in the public comments on our draft report.

To be entirely clear, in all cases we support actions to achieve fair prices that maintain the ability of patients to get the treatments they will benefit from. Our broader view is that when we as a nation give a company a monopoly on a treatment and, instead of "wrestling" with them over coverage, tacitly agree that coverage WILL be provided because we want all patients to benefit, we need some mechanism to suggest an upper limit to the price that a company feels it can charge. It is precisely because access to Trikafta is not and should not be viewed as negotiable that we believe it is essential to use evidence of how much its benefits patients as a guide for its price. When the price of any service throughout the health system is way out of proportion to its ability to improve lives, it can actually cause more unseen harm to other unknown patients -- some with CF, some with other diseases – who can no longer afford their health care.

In closing, we are grateful to the patients who engaged with us -- not just through this recent public comment period, but throughout the past several months. Few patient communities are as committed and as passionate as the CF community. While we may continue to disagree on certain aspects of this review, you have made our work more accurate, and more reflective of patients' lived experiences. Conversations about value and health care always carry a certain level of tension, but we hope you have seen that we have taken a good-faith effort to be evidence-based, patient-focused, and transparent. And we also hope these efforts will help the US achieve a fairer price for these innovative CF therapies, without putting access at risk.

Sincerely,

Steven D. Pearson, MD, MSC

President, Institute for Clinical and Economic Review

David M. Rind, MD, MSc

Chief Medical Officer, Institute for Clinical and Economic Review

#	Comment	Response/Integration
Patient/Patient Groups		
The Boomer Esiason Foundation		
1.	New treatments are able to harness the increased efficacy of combining the two classes of drugs, potentiators and CFTR correctors, and expand treatment options for patients. The most recent FDA-approved combination therapy is the first triple-combination medicine for CF. According to the FDA, the triple-combination therapy expands treatment so that over 90% of patients with CF now have a treatment option. Stunningly, this remarkable, groundbreaking achievement of biopharmacy and science is not mentioned in your 263-page report.	***Thank you for pointing this out. It was originally in the report, but was inadvertently dropped during editing. We have added back a sentence highlighting this important fact in the section of the introduction describing Trikafta.***
2.	We are concerned about the accuracy of this draft evidence report for many reasons, but central to our concern is ICER's use of the quality-adjusted-life year, or QALY. We believe that, as a 2018 article in Health Affairs said, "QALY calculations inherently privilege treatments that extend the lives of those who can be restored to perfect health, and disadvantage the many who seek life-extending treatments despite having a disability or chronic condition that is not curable."	***ICER follows common academic and health technology assessment standards by using the cost per QALY gained, but also presents cost per life year gained and cost per equal value life year gained (evLYG). A recent legal analysis finds the QALY does not disadvantage patients having a disability or chronic condition that is not curable: http://icer-review.org/wp-content/uploads/2020/03/ICER-Analyses-and-Payer-Use-of-Cost-effectiveness-Results-Based-on-the-QALY-and-evLYG-Are-Consistent-With-ADA-Protections-for-Individuals-With-Disabilities.pdf***
3.	But ICER's report fundamentally fails to capture the monumental progress my son has achieved thanks to this triple-combination therapy. Increased pulmonary function is important, but it is the freedom to prepare for a fruitful future rather than to prepare for death that matters most. The larger point here is that the improvements that matter most to patients are not at the center of ICER's cost-effectiveness analysis.	***We modeled Trikafta as a cure and it still did not meet societal norms for cost relative to benefit.***

The Bonnell Foundation		
1.	The CF community also believes ICER wrongly gave Trikafta a low rating based on "a lack of evidence." As a rare and deadly disease, CF therapies will always face limited clinical trial data. To weaponize a lack of evidence against a CF therapy is to discriminate against rare diseases.	***Where there was evidence, we gave it the highest possible rating (A). We gave lower ratings for the group of patients in whom no patients (N=0) have been studied, due to uncertainty arising from the absence of data. The ratings were still favorable, as they indicate that Trikafta is better than best supportive care and at least as good and potentially substantially better than Symdeko.***
2.	Additionally, the FDA granted the therapy orphan drug status; citing limited evidence as a problem undermines the very purpose of the Orphan Drug Act. There is ample evidence to suggest Trikafta will provide benefits for thousands of patients who currently have no or few options. Trikafta has already provided huge, lifesaving benefits to the CF community and I'm thankful to it for giving my daughters a better life. I think about how if I had been born with CF, I would have died around the age my daughters are now. Instead, my daughters' continue to move full steam ahead.	***Again, we gave Trikafta the highest possible evidence rating in the patient groups in whom it has been studied.***
3.	ICER's low rating is an unjust one that could have profound repercussions for patients by blocking access. We hope ICER will reevaluate their methodology and consider the benefits that matter most to patients as well as the nature of CF as a rare disease. Please, ICER, do not make medication access for the CF community any harder than it already is.	***As noted in earlier responses, we have given Trikafta the highest possible clinical evidence rating for all comparisons for which there is evidence, and have given favorable ratings for comparisons for which no evidence yet exists. Similarly, other comment responses note ICER's position that all patients who need these medications should have access to them and that the price of these medications should also be lower.***
Cystic Fibrosis Foundation		
1.	In its final report, the CF Foundation urges ICER to better characterize the potential benefit of long-term modulator use and the limitations of the economic model to capture this benefit; better reflect the impact of this chronic life-threatening disease on daily life; and highlight the limitations of the model in capturing the complexity and heterogeneity of CF.	***We believe that our analysis that models Trikafta as a cure demonstrates that even capturing substantial benefits beyond what has been shown in clinical trials for Trikafta to be considered reasonably priced.***

2.	Modulators mark a significant advancement in cystic fibrosis treatment As noted in the draft report, modulator therapies "substantially improve patient outcomes" when added to best supportive care. These treatments are the first to target the underlying defect in the CFTR protein caused by specific mutations of the CFTR gene. Although each available modulator provides clinically significant benefits to people with cystic fibrosis who are eligible, two modulator drug products — ivacaftor (Kalydeco®) and elexacaftor/tezacaftor/ivacaftor (Trikafta™) — demonstrate such a high magnitude of treatment benefit that CF clinical experts consider them "highly effective modulator therapies" (HEMTs). HEMTs demonstrate dramatic benefits compared to existing therapies across key clinical outcome measures including lung function, growth, risk of pulmonary exacerbations, sweat chloride concentrations, and quality of life. Given the individualized nature of cystic fibrosis, CF clinicians, in consultation with patients, are best positioned to determine which treatment will be most effective for each individual.	***We agree that they represent a huge advance - hence our assessment of high certainty of substantial net benefit. However, even the large magnitude of the benefit fails to justify the price. Other ICER reports have concluded that a drug with the potential to provide cure-like benefits to some patients, and that costs more than $2 million, represented a reasonable value.***
3.	Long-term and real-world data are not yet available for several of these therapies, seriously limiting the utility and reliability of the report The first CFTR modulator, ivacaftor, became available to patients in January 2012, with the most recent approved therapy, elexacaftor/tezacaftor/ivacaftor, receiving U.S. Food and Drug Administration (FDA) approval in October 2019. ICER's review of CFTR modulators so close to the approval date does not allow enough time to collect sufficient data to support a lifetime economic model. Without long-term data, these therapies might be significantly undervalued in ICER's economic model. Although we appreciate ICER's recognition of this limitation in the draft report, we are nonetheless concerned that the results of the economic modeling may be incorrectly interpreted or used by payers, the public, and other stakeholders.	***We agree that we do not have long-term and real-world data yet for the newer CFTR modulators. We tried to make assumptions that biased in favor of the modulators and we also included a curative scenario for Trikafta.***
4.	It is also important to note that ICER's decision to only include studies that have at least 100 participants disregards additional meaningful data. This participant threshold is unreasonable for a rare disease population. Given that each of the three therapies evaluated by ICER is under the rare or ultra-rare condition framework, the high participant threshold for included studies limits the data that contributed to this report.	***We gave Trikafta an A rating based on available data - the highest possible rating. The lower ratings were only in populations with no patients studied (N=0). We requested all available data, and none were available. We are unaware of any additional meaningful data that were not included in the report.***

5.	There is a concerted effort underway in the CF research community to understand the long-term and real-world impacts of modulators on health status, quality of life, health care resource utilization, and other factors. The Cystic Fibrosis Foundation is sponsoring several studies – randomized clinical trial as well as real world research – to evaluate the safety of withdrawing symptomatic treatments, such as dornase alfa, among individuals taking elexacaftor/tezacaftor/ivacaftor. Results from these studies may impact the findings of ICER's report. For more information on these studies, please see the CF Foundation's Research We Fund Highlights Report.	***We apologize for this oversight. We agree and we referenced the study at several places in the report. Please see the last sentence of section 1.5 and the second paragraph of section 6.1. The reference was inadvertently dropped in formatting the draft report. We have added the reference back in.***
6.	Quality-adjusted life years should not be the primary health outcome measurement We would like to again express our concerns about the use of quality-adjusted life-years (QALY) as the primary measure of the cost-effectiveness analysis as QALYs do not account for patient-reported outcomes. We appreciate that ICER acknowledges such limitations and has included additional health outcome measurements such as life years (LYs) and equal value life years gained (evLYGs). However, the lack of patient relevant information in these models cannot be overstated. Furthermore, the QALY looks solely at longevity. The length of life for a person with CF is determined primarily by the degree and decline of lung disease; therefore, by definition, this endpoint disregards all benefits outside of FEV1. QALYs cannot adequately inform coverage decisions or value assessments as they exclude patient experience and other benefits outside of lung function, thus severely limiting this model.	***An individual's, length of life is determined by the mortality equation, which includes variables beyond ppFEV1 (e.g., CFRD, weight-for-age z-score). Modulators have an effect on weight-for-age z-score in the base-case analysis and on CFRD in a scenario analysis. The quality-of-life weights we used in calculating QALYs were derived from EQ-5D responses from CF patients, reflecting patients' preferences for different health states. We include the evLYG and life-years gained as complementary measures to the QALY, while noting that life years gained analyses does not account for patients' preferences for health states with differing quality of life.***
7.	Inappropriate data inputs As we have stated previously, the costs derived from Lieu et al. and Ouyang et al. are not valid estimates for current standard of care. These papers are outdated and should not be generalized in the model. Further, while only utility scores by ppFEV1 are available, we know that modulators have clinical and quality of life benefits beyond lung function. The utility values derived from Schechter et. al are not an adequate measure for modulator therapies as these were developed for use with inhaled antibiotics and are mediated through FEV1. This approach does not account for the clinical and quality of life data necessary for evaluating modulators, which have impact beyond the lungs, thereby imposing significant limitations to the model.	***We use Lieu et al. to inform the differential costs by lung function category and assume that those differential effects persist. We do not use the actual cost values. We ensure that the annual costs are consistent with 2016 data on CF costs (and then updated those costs to 2019 dollars). For QOL we provide results of a validation exercise of our model output to a study that compared mean EQ-5D values among patients treated with Kalydeco with a comparable set of untreated patients and we show that our model is very consistent with those study results.***

8.	Additionally, the use of cost data from different types of payers (private vs. public) for disease management and lung transplant costs poses a noticeable limitation. Costs for private and public payers vary significantly for health care services and therapies. Using a mixture of Truven data and Medicare-specific numbers in the same model causes the resulting cost of CF to be incomparable to what is seen in the real-world and biases model outputs.	***We have changed our analysis to only include costs from private payers. The average annual cost increased from $77,143 to $88,627 (both in 2016 dollars).***
9.	Chronic therapy outcomes should not be discounted 3% per year We disagree with the application of a three percent annual discount rate on health outcomes. This discount rate assumes that one year of life today is valued higher than a year of life in the future. This assumption is philosophical in nature and not grounded in patient experience. While we appreciate the addition of undiscounted scenarios in the Appendix, we have concerns with the use of this discount in the base-case as that is not an appropriate perspective when evaluating chronic disease-modifying therapies.	***Discounting is a standard method in economic modeling. The use of a 3% discount rate in the US as standard for both costs and outcomes has been confirmed in the US by the Second Panel on Cost-Effectiveness in Health and Medicine, and is based on estimates of the real consumption rate of interest and data on real economic growth, which are thought to reflect the social rate of time preference. Note that we present undiscounted results in an appendix to the report.***
10.	Lack of long-term data The timing of this review, and therefore the model, does not account for the anticipated long-term benefits of modulators. As experts in the pathophysiology of CF, we believe that early initiation and long-term use of modulators will have profound implications, altering the course of this disease by preventing downstream disease sequalae including loss of exocrine pancreatic function, structural damage to the lungs, risk of CF liver disease and failure, and CF-related diabetes, which in turn, will have a profound effect on costs to the patient and the system.	***We agree and included a curative scenario to consider a best-case scenario.***
11.	Societal outcomes must be better incorporated into the report. We thank ICER for expanding their outreach to the CF community and their increased diligence in adding the patient perspective to the report. However, ICER has demonstrated that there is no process to incorporate critical patient-reported outcomes or the patient and caregiver experience into the economic model. This is a failing of the model, and thus will create a report that is not inclusive of the true impact of these therapies. As you have heard from people with CF, families, caregivers, and clinicians, CFTR modulators have great potential to dramatically change the trajectory of this disease and, more importantly, individual lives.	***While CF is associated with substantial societal costs, we have limited data on how the use of CFTR modulators may reduce those costs. We received data on the impact of Kalydeco on employment status and incorporated that in our societal analysis. In addition, as noted above, the quality-of-life weights used in calculating QALYs were derived from EQ-5D responses from CF patients, reflecting patients' preferences for different health states.***

12.	Lumacaftor/ivacaftor and tezacaftor/ivacaftor access remain important treatment options Access to lumacaftor/ivacaftor and tezacaftor/ivacaftor remains essential, though they are not considered HEMTs. These treatments are important therapeutic options for people with CF, especially for young children not yet eligible for elexacaftor/tezacaftor/ivacaftor per the FDA label. Further, the clinical impacts of CFTR modulators vary person-to-person and having multiple treatment options available is imperative to extend disease-modifying treatment to as many people with CF as possible. Ultimately, CF clinicians, in consultation with their patients, are best positioned to determine which treatment will be most effective for each individual.	***We agree.***
13.	Coverage policy landscape of CFTR modulators We appreciate ICER's attention to coverage policies for CFTR modulators as the value of these therapies is only realized if patients can access them. While many of the plans reviewed in ICER's evidence report provide coverage aligned with the FDA's label, there are multiple plans included that have implemented more restrictive coverage criteria. Many of these criteria are clinically inappropriate, administratively burdensome, and create unnecessary barriers to access. ICER's previous report on CFTR modulators stated that "public and private payers should continue to affirm their commitment to provide access to important clinical advances for CF and should remove superfluous requirements for coverage approval and continuation." This statement from ICER's earlier analysis summarizes these important facts and should be included in the current report.	***This language was included as part of the policy recommendations chapter of the prior report, which describes discussions that take place during the public meeting. As this event has not yet taken place, it would be premature for us to include such language in the draft assessment. That being stated, we continue to agree that superfluous requirements in CF coverage policies are inappropriate and anticipate the final report will have such language.***

Cystic Fibrosis Lifestyle Foundation		
1.	The evidence of this belief is the report referencing the incorporation of input from community organizations, yet a complete absence that ALL organizations expressed disapproval and objection to the work of ICER. That is manipulation. The interest being served by this report and process is clearly not that of the patient's. A collective objection was made overtly clear on the January 17, 2020 phone call between ICER and CF community representatives, which was completely discarded by the report.	***The call in reference was a group discussion among CF patients and caregivers to hear about their experiences with the disease and its treatment, particularly the long-term effects of treatment that have not been well described in the clinical literature. It was neither the intent nor objective of the call to gather feedback or perspectives on ICER's process, so it would have been inappropriate for us to summarize these comments.*** ***Furthermore, the comments in reference reflected a misconception of ICER's work and goals. As noted in other responses, ICER has been consistent in its stance regarding access: all CF patients should have access to treatments that work for them, and the treatments should be priced reasonably. We describe in the draft and revised report the root concern we believe this commenter is referring to - that CF patients experience substantial barriers to care, whether due to costs or insurance restrictions.***
2.	While the report appears comprehensive from the attempt at incorporating the lived experiences of physical, psychological, social, emotional, treatment burden and quality of life benefits, there is no clear numerical factoring of these outcomes in the QALY assessment process. The severe limitation of selected endpoints in and of itself disqualifies the legitimacy of this statistical analysis	***We agree that certain lived experiences of CF patients cannot be (or have not been) quantified in a way that can be incorporated into our analysis. We provided a sensitivity analysis on HRQoL gains (including a curative scenario) to convey the implications of different assumptions. While the results did vary somewhat across the sensitivity and scenario analyses, none of the analyses produced results that were below commonly-used cost-effectiveness thresholds.***

3.	Another severe limitation of this process is in the fact that CF physicians with direct clinical experience and intimate engagement with families faced with the challenges of CF were merely consulted for input, but were not an integral part of the evaluation process, formulary development or outcome assessment. Self-establishing ICER as a definitive expert on valuating patient lives and treatment worth in the absence of practical, clinical and empirically based experts in the disease state is yet another reason for disqualification. As was demonstrated with input from community organizations, and most likely from physicians, ICER chose what input was useful or not, and effectively manipulated data through contrived statistical formulas to achieve the desired outcome.	***We disagree that CF patients and clinicians have not been an essential to our process. Descriptions of how we sought input from patients and incorporated their feedback in the report are present in Chapter 2. We have worked closely with practicing CF experts throughout the review process, including research design, interpretation of results, and review of our draft report. We are unsure what the commenter means when referring to "formulary development." ICER does not place a value on the life of patients, we look at the value of a treatment. Our research methods follow established best-practices and we have noted no clinical expert objection to our interpretation of the evidence, which is that these drugs provide substantial benefits to patients.***
Cystic Fibrosis Research, Inc.		
1.	Unethical Use of Quality Adjusted Life Year (QALY): There are many mutations of the CFTR gene that causes cystic fibrosis, and individuals with CF have extremely varied disease expression. The report does little to address the heterogeneous nature of the disease and its significance upon drug impact. Our impression is that to do so would to make evident the many flaws related to the use of the Quality Adjusted Life Year (QALY) in your analysis. The utility weights used to determine an individual with CF's QALY, based on ppFEV1, is simplistic, and fails to address the complex impacts of the disease. ICER's use of a cost-benefit analysis utilizing the Quality Adjusted Life Year and equal value of life-year gained negates the value of the report in its entirety. The use of QALY is a discriminatory methodology that will always penalize individuals with disabilities, and specifically those with incurable chronic diseases such as cystic fibrosis.	***Our report does not estimate QALYs (or evLYGs) for individuals.***

2.	To place a numerical value on the lives of those with cystic fibrosis in order to determine drug pricing is unethical, and leads one to ponder others in history who have done the same with catastrophic impacts. We do not agree with your organization's claim that its use of QALY to determine drug price value is not inextricably related to placing a value on the lives of those most needing the drugs.	***As we have stated numerous times in the past, ICER does not attempt to place a value on human life. We are evaluating whether the price of a drug is appropriate for the level of health gain it provides, as is done in most developed health systems across the world. The use of the QALY allows ICER and others to recognize when a drug improves quality of life: we believe that a drug that improves both quality of life and length of life is more valuable than a drug that only improves length of life.***
3.	CFRI and its constituents were shocked by the following sentence in the report: "As an extreme scenario analysis, we evaluated Trikafta as a curative therapy and found that the cost-effectiveness ratio of lifetime therapy with Trikafta continued to far exceed commonly used cost-effectiveness thresholds even under the assumption that it maintained individuals with CF in normal health such that they never experienced any symptoms or complications of CF." Countless members of the CF community were alienated by that conclusion, which essentially informed those desperately in need of the therapy that they are not worth the cost.	***We acknowledge that it can feel personal and uncomfortable to talk about what the price should be for a cure of a life-shortening and disabling condition, especially for one that afflicts children. Nonetheless, we feel it can help give perspective when there are uncertainties about how well a model is capturing the health benefits of a treatment. This kind of analysis allows us to ask whether, even if the model were not capturing all the benefits that patients get from treatment, the price being charged could possibly be viewed as fairly scaled to its benefits. This is always a helpful way to "test" a model's judgment about fair pricing, but it's also particularly important to evaluate when there is limited or no competition, and insurers trying to negotiate over pricing can't walk away from the table because the treatment is a "must cover" kind of drug. Manufacturers in this situation have great discretion over the price they set, and if a manufacturer set the price for a cure of any condition at $100M or even $10M, we suspect that many patients and families would find the price excessive. The question then becomes what price reflects the top amount we can spend that would reward innovation and the good received by patients and their families who benefit from a treatment without doing ultimately more harm by the effects on insurance cost increases that force people to drop***

		insurance or delay or forgo care. That's what this exercise in pricing analysis is meant to explore, and we hope you understand that our underlying motive is to push the limits of our model so that we can make sure we aren't potentially mislabeling a price as too high.
4.	Flawed Economic Analysis: We are very concerned by the economic analysis used in the report that appears to have multiple flaws leading to an overprediction of medication cost over time. Most notably, we question why you utilize static pricing to project a lifetime of use of Trikafta, without considering the landscape of the CF therapeutic pipeline. There are other companies in clinical trials with CFTR modulators. There is future potential for generics. In addition, there are numerous companies exploring genomic editing, and mRNA therapies. It is highly unlikely that Trikafta will remain the only option in the not-so-distant future. By assuming decades of use with static pricing, you have assigned a cost that is not based in reality.	***As is consistent with best practices at international HTA agencies and with the great preponderance of academic work in health economics, ICER's cost-effectiveness analyses do not routinely make estimates of price changes across comparator treatments linked to patent and exclusivity time horizons, given the unpredictability of these changes in the US health care market.***
5.	We continue to be concerned that ICER fails to accurately assess the full array of medical costs associated with the multi-faceted management of the disease. Cystic fibrosis care runs in the hundreds of thousands of dollars per year per patient. ICER's analysis also fails to include the related loss of income caused by the disease – both for adults with CF and for the parents of children with cystic fibrosis. In addition to reduced medical costs due to reduced exacerbations, hospitalizations and transplantation, a therapy that potentially enables individuals with CF as well as CF caregivers to work has far broader financial implications.	***We include average annual costs from a published study. While some patients may experience hundreds of thousands of dollars per year our analysis is not meant to apply to individual patients but to a population of patients. We were able to obtain confidential confirmation from two private payers that our cost estimates are largely consistent with their estimates. We have, however, updated the cost input in the revised report to reflect costs paid by private insurers, as noted in an earlier comment response.***
6.	It would require far more than this imposed three-page limit to share the stories of success with Trikafta, including improved lung function, reduced dependence on insulin, reduced hospital stays, fewer exacerbations, improved weight gain, and improved mental health. You have heard from numerous patients and CF advocacy groups, but the life-changing impact of this therapy for many is not conveyed in your draft report.	***We note that each of these considerations is discussed qualitatively in Chapter 2 of the report, and those for which data are available are reflected in the clinical and economic analyses in subsequent sections of the report. There is a five page limit on draft report comments, not three.***

7.	CFRI and its constituents have deep concern that your report will give credence to state and private payers who seek to reduce costs by keeping vital therapies out of the hands of those who would benefit from them. Life with CF is a daily battle to slow the disease's progression. Prior to the arrival of CFTR-modulating therapies, the decline in lung function was inevitable, regardless of one's adherence to the time-consuming daily CF medical regimen. CFTR-modulating therapies – most notably Trikafta – have brought realistic hope that the downward course of the disease can be halted, and health improved. It would be a travesty should the draft Evidence Report be used to deny access to these medications by those who desperately need them.	***As we have noted in other responses and public statements, ICER's position is that all patients who stand to benefit from these therapies should have access to them, and our work should not be used to support efforts to the contrary. At the same time, we believe our analyses demonstrate that current prices for these therapies exceed their demonstrated benefits. This suggests the costs of these therapies should be reduced to an appropriate level, while continuing to provide access to all eligible patients.***
8.	Potential to Halt Innovation and Drug Development: Equally frightening to us is the reality that should your flawed analysis be embraced by payers to deny access to CFTR-modulator therapies, there will be a chilling effect on innovation in the biopharmaceutical industry. It is a tragedy that approximately 10% of those with cystic fibrosis are unable to benefit from these therapies due to their specific CFTR mutations. There are others with eligible mutations who cannot use Trikafta for a variety of reasons. ICER continues to disregard the unique challenges faced by the cystic fibrosis community and other rare disease groups to entice biotech companies to enter the rare disease realm. Our community is still suffering, and for those without new therapies, facing an early death is a horrific reality.	***ICER has not found that our reports are chilling innovation. We believe that when drugs are fairly priced, this supports both fair access and future innovation.***
9.	It is a challenge to incentivize research and drug development for those with CF. This report has the potential to provide payers with a justification to discontinue coverage for new and innovative therapies, with a cascade impact of suppressing research, and discouraging investment in new drug discovery and development. This would be catastrophic for the cystic fibrosis community, and has broad implications for other rare disease groups.	***See above response.***

Don Maurice Kreis		
1.	When we turn to investor-owned businesses to provide essential services, whether it's the energy that heats and lights our homes or the drugs that extend lives and abate suffering, this reliance has, or ought to have, two key consequences. First, devoting private capital to these endeavors should yield innovation and quality improvement. Second, the public should not be exploited because profit must be reasonable and prices not excessive. Vertex Pharmaceuticals has clearly succeeded with the first objective while acting in contempt the second. As noted at page 10 of the Draft Report, Vertex "declined to participate in the review process" despite having been invited to "submit relevant information on research, development, and manufacturing costs that may impact pricing of a drug." From an investor perspective, return is linked to risk – which is why drugs like Kalydeco, Symdeko, and Trikafta should be expensive. ICER should revise the Draft Report to explain and to acknowledge this reality of market economics, the better to hold Vertex accountable. The pharmaceutical company's obduracy supports an inference that its modulator prices yield profits beyond even the lofty ones its investors should reasonably expect. But Vertex is not just failing to cooperate; it is supporting an 'astroturf' (i.e., fake grassroots) organization known as the Cystic Fibrosis Engagement Network that publicly condemns any use of any cost-benefit principles to evaluate the fairness of prices for modulators. See, e.g., CFEN video presentation "What's Wrong With ICER?," complaining that "sometimes economists can have more control than your doctor about whether you get the medicine that treats your condition" and arguing that "doctors, not economists, should be the ones deciding which medicines patients get").	***We agree that market dynamics are an important part of the conversation of the value of these drugs. Because such dynamics are open to interpretation, we include them in the policy roundtable discussion that takes place during the public meeting where we can more thoroughly discuss various perspectives. Any recommendations or comments from ICER on market dynamics will thus be reserved for the final report that will be released after the meeting.***

2.	Both the authors and the readers of the Draft Report should know that not all Cystic Fibrosis Families condemn the use of cost-benefit analysis to evaluate from a demand-side perspective the propriety of charging $312000 a year for a breakthrough medication – especially when the company that owns the medication refuses to supply any information that would support a supply-side evaluation of the price. The Draft Report should be clarified so as to explain forthrightly that when CF patients ask their neighbors (be they coworkers in the case of employer-provided health insurance or fellow taxpayers in the case of Medicaid) to share the financial burden of an ultra-expensive medication, this is not a matter of letting bean-counters (i.e., economists and statisticians) rather than doctors and other empathetic caregivers make treatment decisions. It is, rather, an acknowledgement that when society pays for a good, its value must be assessed from a societal perspective.	***Thank you for these comments. See above for a more detailed response regarding how ICER incorporates these considerations into its public meetings and final report.***
3.	Overall, the Draft Report lacks clarity and therefore persuasiveness, particularly for a cystic fibrosis community that is understandably concerned that the ICER analysis could be used to deny CF patients access to modulator therapies. Although the early sections of the Draft Report do a good job of explaining cystic fibrosis and its consequences – thus confirming that ICER knows how to reduce a complicated scientific story to its essentials while writing with empathy – Chapter 5 of the Draft Report can be charitably described as inaccessible to those without advanced training in statistical analysis. This is profoundly regrettable given that Chapter 5 is the heart of the ICER analysis.	***We have edited Chapter 5 with these comments in mind. We now provide an introduction to health economics modeling in the first section and have moved some of the technical language to the appendix (i.e., mortality equation details), replacing it with what we hope to be more user-friendly language. This version of the report also includes an executive summary that describes our analyses at a less technical level.***
4.	I am suggesting that when the report's key chapter is virtually impossible to understand for someone like the undersigned (who holds a bachelor's degree, a masters degree, and a juris doctorate, and who has pursued a legal specialty that requires immersion in principles of finance, accounting, and engineering, and who has for the past 18 years of CF parenthood been studying the disease and its public policy implications) then ICER's analysis of the modulator therapies is vulnerable to being dismissed and ridiculed by those who simply cannot understand what ICER is attempting to communicate. To the turgid analytical prose of Chapter 5 should be added introductory and concluding sections that explain this section's analysis in summary fashion, using language sufficient to be understood at least by college educated non-mathematicians/statisticians.	***Along with an introduction to health economics modeling in the first section of chapter 5, we have included revised introductory and concluding sections, and have added an executive summary that summarize the analyses with less technical detail.***

5.	In 2018, with much fanfare, ICER announced that it would supplement its reliance on cost per quality adjusted life-year (QALY) with analysis of cost per Equal of Life Year Gained (evLYG). As the Cystic Fibrosis Foundation noted in its October 21, 2019 scoping comments, "QALYs do not account for patient-reported outcomes" and, thus, it is laudable that ICER "will acknowledge such limitations under the framework for ultra-rare diseases and incorporate[] the [evLYG] as an additional effectiveness measure." As ICER is surely aware, this is a muted form of similar criticism that ICER has received from other, more outspoken quarters of the CF community. See, e.g., February 24, 2020 blog post of CF patient-advocate Gunnar Esaison entitled "How Do You Value Your Life With Cystic Fibrosis?" (in which Mr. Esiason, who uses Trikafta, concludes: "I can't help but look at that [QALY] mortality function and laugh" and ridicules bioethics as not a "real profession").	***The quality-of-life weights we used in calculating QALYs were derived from EQ-5D responses from CF patients, reflecting preferences for different health states. Because the QALY records the degree to which a treatment improves patients' lives, treatments for people with serious disability or illness have the greatest opportunity to demonstrate more QALYs gained and justify a higher price. We include the evLYG and life-years gained as complementary measures to the QALY, while noting that the latter does not account for patients' preferences for health states with differing quality of life.***
6.	How regrettable, then that ICER buries its analysis of evLYG in the Draft Report. Indeed, "evLYG" does not even appear in the list of abbreviations at pages vi-vii of the Draft Report. There is no real discussion of evLYG in Chapter 5. It merely becomes clear (via review of Table 5.10 at page 76) that the modulator therapies under review become only slightly more cost-effective when the relevant metric is cost per evLYG rather than cost per QALY gained. It is almost as if ICER cannot bring itself to acknowledge that the evLYG is an important metric – a squeamishness that you should overcome, in my respectful opinion.	***The abbreviation evLYG was inadvertently left out of the list of abbreviations and has been added to that list in the revised report. The evLYG results are summarized in the report, and we have added more discussion of these to the revised report.***
7.	Section 5.2 of the Draft Report makes clear that a key driver of CF treatment costs is are acute pulmonary exacerbations, defined as "those that involve treatment with IV antibiotics either in the hospital or with home treatment." Draft Report at 59. This may be problematic to the extent avoided acute pulmonary exacerbations is a key benchmark. Over my 18 years as a CF parent, I have learned that the decision on whether to diagnose an acute pulmonary exacerbation is entirely subjective; a patient with a ppFEV1 at or near 100, with no history of colonization by pseudomonas aerugenosa, in the dead of winter, is at higher 'risk' of going on IV antibiotics than a patient in July who is itching to be outdoors, is used to living with p. aerugenosa, and has recently endured a similar inpatient stay. ICER should consider analyzing the cost of CF care, with or without modulators, on a cost-per unit of ppFEV1 improvement basis even if, as the Draft Report suggests, these costs apparently vary depending on other factors. See id. ("disease management costs varied by level of ppFEV1") and Draft Report at 51 ("the impact of an absolute increase of 5% in a	***We added language to clarify why we chose this definition for pulmonary exacerbations (to match the definition used in the literature linking pulmonary exacerbations to CF-specific mortality). For a cost-consequence measure, we used cost per pulmonary exacerbation averted instead of cost per unit of ppFEV1 improvement, because CFTR modulators have an impact on pulmonary exacerbations above and beyond what would be predicted by changes in ppFEV1 alone.***

	patient with a baseline ppFEV1 of 40% likely differs from that of a 5% increase in a patient with a baseline of 90%").	
8.	The estimate in the Draft Report of the cost of best supportive care is rendered in frustratingly opaque fashion and does not comport with the lived experience of my family. According to page 69 of the Draft Report, the average annual cost of best supportive care in 2016 was $77,163, which was "used to calibrate the best supportive care cost estimates prior to updating to 2019 dollars." Table 5.6 on the following page suggests that for a patient younger than 18, the direct cost of CF care, for both "disease management" and pulmonary exacerbations, is $81,271 in 2019 dollars. Please revise the Draft Report to include a lucid explanation of how the 2016 cost estimate was used to "calibrate" (if not determine) the 2019 estimates. According to reimbursement records provided by my family's health insurance provider (Anthem Blue Cross Blue Shield) and prescription drug plan (Express Scripts), in 2019 my daughter incurred $140,767 in prescription costs last year and a comparable sum in healthcare costs. From our perspective, this was a routine CF year – one that included a single two-week inpatient stay to treat a pulmonary exacerbation. This suggests your estimate of the cost of best supportive care may be seriously in error, which bolsters the argument for a more rigorous and publicly disclosed analysis.	***We added language clarifying how we derived cost estimates for best supportive care. In addition, we received confirmation from two private health insurance payers that the annual costs we are using are reasonable compared to their average paid amounts for CF care. We also note that this cost is varied across a range of values in the sensitivity analyses in the report.***
9.	Finally, the Draft Report states that because Trikafta has an eliglble patient population of greater than 10,000 individuals, the ICER "ultra-rare" framework did not apply and thus threshold prices were calculated only for cost-effectiveness thresholds less than $200,000 per QALY. Draft Report at 55, 86. In the interest of analytical rigor and making the final report as persuasive as possible, ICER should analyze Trikafta under both the "ultra-rare" framework and its regular framework. At the very least, ICER should explain this arbitrary distinction between drugs that qualify for the ultra-rare framework and those that do not.	***Definitions of "orphan" or "rare" and "ultra-rare" conditions vary widely across organizations around the world. Small patient populations may make it difficult to conduct studies that would demonstrate with the same level of certainty the effectiveness of an emerging drug, and may make it impossible to recoup development costs. It is ICER's experience, confirmed in discussions with HTA agencies around the world, that the ability to mount RCTs with adequate outcome measures, duration, and follow-up appears to be maintained until the candidate population size drops below a prevalence of approximately three per 100,000 population (about 10,000 individuals in the US). Given that Trikafta has an eligible population much higher than this, our decision to evaluate it under ICER's standard Value Assessment Framework remains unchanged.***

10.	The portion of that price presently attributable to Vertex Pharmaceuticals is almost certainly too high, but this cannot obscure the nobility and virtue of what this company's work, in concert with the CFF, has accomplished. As a CF family whose miracle medical breakthrough is still ahead of us, we hope the ICER process succeeds in making future breakthroughs more likely and more accessible to all who will benefit from them. It is imperative, and ICER should stress, that in no circumstances should any aspect of this process lead to therapies becoming unavailable to patients who will benefit from them.	***We agree and this position is reflected in ICER's prior work in CF. In his opening remarks at our last meeting, ICER's President noted that denying coverage of these therapies is not an option, and this was reflected in the recommendations in our Final Report. Our stance has not changed. The conclusions of our prior report, and of the current evidence report are that these medications are essential for eligible patients, but that their current prices exceed what health systems typically consider to be appropriate for their level of benefit.***
Emily's Entourage		
1.	Discriminatory methodology The QALY unfairly devalues the lives of those with disabilities, including fatal, incurable chronic illnesses like CF. The report fails to capture the complexities of CF and its varied clinical presentation and impact on patients' and caregivers' lives. Focusing on ppFEV1 provides an oversimplified, inaccurate view of the disease that does not reflect individuals' live experience with CF. In addition, use of the QALY to determine treatment coverage is prohibited by Medicare. For Medicaid, it would violate the Americans with Disability Act (ADA) by engaging in a discriminatory process for evaluating coverage decisions and limiting access to life-saving treatments for disabled individuals, according to a recent analysis of QALY and the ADA by The Pioneer Institute.	***We agree that focusing on ppFEV1 and the respiratory domain of the CFQ-R fails to fully capture the lived experience of patients with CF. We highlight this in the Insights Gained from Patients section of the report and in the Controversies and Uncertainties section. We encourage advocates, like Emily's Entourage, to make this case to the FDA and Vertex so that more robust measures that capture the patient's experience are included in both randomized and observational studies of CF and therapies for CF, such as Trikafta. The foundation for the ICER process is evidence and without evidence there is uncertainty. Advocating for additional, high-quality evidence is essential in order to capture the full value of modulator therapies such as Trikafta.*** ***Regarding the ADA, we refer the commenter to a recent legal analysis that finds no such discriminatory impact: http://icer-review.org/wp-content/uploads/2020/03/ICER-Analyses-and-Payer-Use-of-Cost-effectiveness-Results-Based-on-the-QALY-and-evLYG-Are-Consistent-With-ADA-Protections-for-Individuals-With-Disabilities.pdf***

2.	Flawed economic review ICER's economic review of Trikafta is flawed in a number of ways, which call into question its final results. First, the cost effectiveness calculations include the full list-price of Trikafta over a lifetime, which is not realistic on the basis of generic entry, new and improved drugs, and cures. When Trikafta goes off patent, the price will come down substantially. Without factoring in the price reduction with generic entry, the model is based on a full list-price that is time-limited and the cost projections are inaccurate.	***As is consistent with best practices at international HTA agencies and with the great preponderance of academic work in health economics, ICER's cost-effectiveness analyses do not routinely make estimates of price changes across comparator treatments linked to patent and exclusivity time horizons, especially given the unpredictability of these changes in the US health care market.***
3.	In addition, the model unfairly penalizes Trikafta for extending life and attributes the consequent disease management costs to this therapy. If all costs are included in the model, then projected benefits should be too, including the projected productivity and impact of patients who are not getting sicker as well as alleviated caregiver burden and employment opportunities.	***We model both the benefits and the costs of extending life, as is appropriate. While the CFTR modulators do reduce the BSC costs each year, these costs are applied for a longer period of time for those treated with CFTR modulators because of the large increase in life expectancy for these patients. We conducted two important scenario analyses for Trikafta. In one we assumed that disease management costs were reduced by an additional 75%, and in the other we assumed a curative assumption where the only costs were of Trikafta.***
4.	Finally, discounting health benefits devalues therapies like Trikafta that extend life by long periods of time. While achievement of long-term life extension is a benefit that should be celebrated, instead discounting health benefits systematically disadvantages therapies that treat chronic, genetic diseases like CF where the model starts at a young age.	***Discounting is a standard method in economic modeling, used to reflect the social rate of time preference, based on estimates of the real consumption rate of interest and data on real economic growth. The use of a 3% discount rate in the US as standard for both costs and outcomes has been confirmed in the US by the Second Panel on Cost-Effectiveness in Health and Medicine. Note that we present undiscounted results in an appendix to the report.***

5.	Stifling of innovation for remaining 10% EE represents those with CF nonsense mutations who do not benefit from the existing modulator therapies, a group in which I personally belong. Those of us in the outlying 10% still suffer from the same fatal, devastating disease that CF has always been. We continue to wait—with bated and fading breath—for advances that benefit our CFTR mutations. With a disease that advances despite our hardest efforts to delay it, it is a race against time for the outlying 10%. The findings of the Draft Evidence Report will have a stifling effect on future innovation, disincentivizing companies from investing in therapeutic development for the final 10%. Stymying innovation for the final 10% will result in suffering and death, not to mention significant burden and loss of productivity among individuals with CF and caregivers. In addition, the downstream effects of this report will not only result in reduced drug development for the final 10% of CF patients without modulators, but those effects will extend across all rare diseases. Individuals with rare diseases often represent the extremes of disease and innovation originally developed for these populations has the potential to scale far beyond the rare disease population, benefitting far larger swaths of the population, which is not accounted for in the ICER report.	***ICER has not found that our reports are chilling innovation. We believe that when drugs are fairly priced, this supports both fair access and future innovation.***
Institute for Patient Access		
1.	Evidence Ratings Fail to Account for the Triple-Combination Therapy's Originality and the Fact that Cystic Fibrosis Is a Rare Disease ICER's evidence ratings are not objective measures. Rather, the ratings reflect researchers' judgement regarding two attributes: (1) the estimated clinical benefit of the drug; and, (2) how certain the researchers are of the drug's clinical benefit. The scores are, consequently, ICER researchers' subjective assessment of the existing evidence. In this case, the draft evidence report acknowledges that, based on the evidence, all of the combination drugs under consideration improved patient outcomes. The report also notes that the adverse side effects from the medicines were mild and uncommon. It is reasonable to conclude that efficacious medicines with minimal side effects should be rated highly. Yet the draft evidence report instead assigns triple-combination therapy a B+ and C++ evidence rating for two of the comparisons.	***We gave Trikafta the highest evidence rating (A) in both the populations in which it was studied: high certainty of substantial net health benefit versus both best supportive care and Symdeko. It is not possible to conclude the magnitude of benefit with high certainty in a population of patients in whom the drug has not been tested (heterozygous F508del with residual function mutation). One could argue that an I (insufficient evidence) is the most appropriate evidence rating given the complete lack of evidence. However, we gave it a C++, which indicates that we judge it to be at least as beneficial as Symdeko and to have the potential to be substantially better than Symdeko.***

2.	The report justifies these subjective ratings by noting, several times, that there are insufficient published randomized trials or observational data for triple-combination therapy in the relevant populations. In short, the available data is encouraging, but relatively little of that data is available at this point. As ICER surely realizes, there is limited data about triple-combination therapy because cystic fibrosis is a rare disease and because the drug was approved by the FDA only as of October 2019. The draft evidence report's low assessment of triple-combination therapy, therefore, essentially penalizes the treatment for being a new orphan drug that treats a rare disease.	***This comment is inaccurate. We gave A ratings for small subgroups of patients with CF. We only gave lower ratings for populations with no patients (N=0) studied. The lower rating was not a statement about the net health benefit; rather it reflects substantial uncertainty due to the complete lack of evidence in this subgroup of patients. There was no penalty due to a small patient population: see the A ratings that were given in populations with low numbers of patients.***
3.	Triple-combination therapy was granted orphan drug status by the FDA's Office of Orphan Products Development to encourage the development of treatments for cystic fibrosis. By failing to acknowledge the reality of new orphan drugs, the draft evidence report undermines the important goals of the orphan drug program. ICER's subjective assessment is particularly troubling because a low evidence rating could suggest that the drug is less effective. Not only is there no evidence to justify such a supposition, there is ample reason to expect that triple-combination therapy will provide a significant benefit to many cystic fibrosis patients. In sum, the low evidence rating is inappropriate and could unjustifiably reduce patients' access to triple-combination therapy.	***Again, the lower evidence ratings reflect uncertainty about the net health benefit of Trikafta in populations that have yet to be studied. There are neither case series nor RCT data for these patients. However, we did conclude that it is at least as good, and likely better than Symdeko and definitely better than best supportive care.***
4.	…a novel treatment available to most cystic fibrosis patients, including adolescents, who previously had no options and giving others in the cystic fibrosis community access to an additional effective therapy," said acting FDA Commissioner Ned Sharpless, M.D. "In the past few years, we have seen remarkable breakthroughs in therapies to treat cystic fibrosis and improve patients' quality of life, yet many subgroups of cystic fibrosis patients did not have approved treatment options. That's why we used all available programs, including Priority Review, Fast Track, Breakthrough Therapy, and orphan drug designation, to help advance today's approval in the most efficient manner possible, while also adhering to our high standards. The FDA used "all available programs" to expedite triple-combination therapy's approval for a reason. Expanding the share of patients with an effective treatment to 90% of the population is a significant benefit. The draft evidence report fails to demonstrate that the analysis considered these benefits when evaluating triple-combination therapy, which is particularly concerning with respect to the cost-effectiveness models. Without accounting for the expansion of patients who now have an effective treatment, the cost-effectiveness models are, by design, undervaluing triple-combination therapy	***Again, we highlighted the remarkable benefits of Trikafta for the patients with CF mutations in which it has been studied. An A rating. Please note that priority review, fast track, orphan drug, and breakthrough therapy designations are given before data from pivotal trials are available. Some therapies with these designations never are FDA approved or are found to be of no benefit. Additionally, the models did account for the "expansion of patients who now have an effective treatment".***

5.	The draft evidence report acknowledges this problem by stating that "economic models such as the ones used in this analysis cannot capture the full range of quality-of-life effects associated with the disease, or the improvements in quality of life experienced by CF patients taking CFTR modulator therapy." Quality-of-life measures are difficult, but important, to quantify. Cystic fibrosis patients generally rate their quality of life as low, and they highly value medicines that can reduce their daily burdens and increase their quality of life – even small improvements to their quality of life are valued highly. Since the economic models fail to capture these important unquantifiable benefits, the long-term cost-effectiveness calculation significantly undervalues the benefit these treatments offer patients.	***We agree and acknowledge in our report this limitation. We present a sensitivity analysis on the quality-of-life measure and report the results where we assume that the quality-of-life effect is increased by 50% of what was demonstrated in a study of the quality of life effect of Kalydeco (Bell et al.). In addition, we present a hypothetical curative scenario analysis under which modeled patients are restored to full health, which would encompass more than the expected range of potential benefits from therapy.***
6.	The QALY Methodology Is Inappropriate for Rare Diseases According to the draft evidence report, "the primary health outcome was quality-adjusted life years (QALYs) but we also report life expectancy in life years (LYs), equal value life years gained (evLYGs) and the lifetime number of acute pulmonary exacerbations." While reporting on other factors is a positive development, the "primary health outcome" drives the conclusions drawn from the report. QALYs have well-documented weaknesses, particularly for rare diseases, that make this methodology inappropriate for evaluating the cost effectiveness of cystic fibrosis medications. As evidence of these weaknesses, a recent report by the Pioneer Institute argues that the use of QALYs may violate several legal provisions of the Americans with Disability Act (ADA)	***ICER follows common academic and health technology assessment standards by using the cost per quality-adjusted life year (QALY) gained as the primary measure of cost-effectiveness, but also presents cost per life year gained and cost per equal value life year gained (evLYG). The QALY is the gold standard for measuring how well a medical treatment improves and lengthens patients' lives, and has served as a fundamental component of cost-effectiveness analyses in the US and around the world for more than 30 years. For ultra-rare conditions, ICER acknowledges and highlights additional uncertainty in translating patient outcomes into QALY measures. Regarding the ADA, we refer the commenter to a recent legal analysis that finds no such discriminatory impact: http://icer-review.org/wp-content/uploads/2020/03/ICER-Analyses-and-Payer-Use-of-Cost-effectiveness-Results-Based-on-the-QALY-and-evLYG-Are-Consistent-With-ADA-Protections-for-Individuals-With-Disabilities.pdf***

7.	Another relevant concern about QALY methodology underscores why it is inappropriate for evaluating cystic fibrosis treatments. People living with cystic fibrosis have severely restricted lung function that reduces their endurance. Patients have indicated that clinically small improvements in their lung function can meaningfully improve their quality of life. QALYs, however, are designed to undervalue improvements that may be clinically small, even if they are meaningful for patients in everyday life. Beyond these foundational problems with QALY methodology, the draft evidence report also inconsistently applies the QALY methodology by using a lower range for the cost-effectiveness threshold for triple-combination therapy ($50,000-$200,000 per QALY) than for two other therapies evaluated ($50,000-$500,000 per QALY). There is no sound justification for using a different cost-effectiveness threshold across medicines that treat the same patient population.	***The quality-of-life weights used in calculating QALYs rely on individuals' preferences for different health states. Because the QALY records the degree to which a treatment improves patients' lives, treatments for people with serious disability or illness have the greatest opportunity to demonstrate more QALYs gained and justify a higher price. ICER's provision of different cost-effectiveness ranges for treatments of ultra-rare populations is not an endorsement of using different thresholds, but an acknowledgement that decision-makers often give special weighting to other benefits and contextual considerations that may lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.***
Partnership to Improve Patient Care		
1.	We have noted in the past that the QALY disservices those with chronic and disabling conditions, as it is fundamentally designed to undervalue what may be deemed clinically small improvements. The ability of novel treatments to bring improvements through increased efficacy or the reduction of side effects, regardless of whether they are perceived as clinically significant, can substantially improve quality of life for patients with CF. This is particularly applicable to CF patients in regard to lung function. Even small improvements in lung function can increase a CF patient's endurance and ability to participate in day-to-day activities, such as attending work or school. The QALY undervalues these improvements and thus does not paint an accurate picture of the value of these treatments to patients.	***The quality-of-life weights used in calculating QALYs rely on individuals' preferences for different health states, and are intended to reflect differences that are meaningful to patients' quality of life regardless of perceptions of clinical significance.***

2.	The use of this limited metric also presents an incredibly narrow view to measure CF progression over time. ICER's model only measures the treatments' effects on lung function, weight, and acute pulmonary exacerbations, when we know there are many other outcomes that matter to patients with CF. There are tools and data available to capture a more robust picture of disease progression and quality of life for CF patients. If ICER's goal is truly to capture the value of these treatments, it should not use the EQ-5D as the patient-reported outcome tool for this assessment. The quality of life of patients with CF is better measured with the Cystic Fibrosis Questionnaire – Revised (CFQ-R), which assesses 13 domains relevant to patients living with CF, compared to a mere five domains associated with the EQ-5D. Most importantly, given that QOL in the ICER model is linked directly to a measure of lung function, studies have shown both considerable variance in quality of life across stages and severity of disease, but also across the many aspects of QOL that the disease affects beyond lung function, in particular nutrition, depression and anxiety. It is imperative that ICER utilize the CFQ-R or other disease-specific instruments when assessing these treatments. Furthermore, ICER should ensure that all outcomes are mapped back to the QALY.	***The evidence review reports on the effect of CFTR modulators on the CFQ-R scores. Many of the trials only reported on the respiratory domain of the CFQ-R and not the other 12 domains. While there is a mapping function from CFQ-R to EQ-5D scores it requires individual level data, which we do not have. We conducted a validation exercise to show that our model output validates well to a study that compared mean EQ-5D scores of patients treated with Kalydeco compared to similar patients not treated.***

3.	ICER's CF report makes the incredibly concerning assessment that even if Trikafta were found to be curative, it would still not be cost-effective. In saying this, ICER makes clear that it is very willing to put a price on a human life, which is devastating to the patient community, and which we believe would be incredibly troubling to society writ large. We do not disagree that prices should be set in a reasonable manner and that we should be having a robust discussion about what that looks like in an era of disease-modifying and curative therapies. We also feel that finances being prioritized over a patient's life is an inappropriate starting place for this conversation.	***We acknowledge that it can feel personal and uncomfortable to talk about what the price should be for a cure of a life-shortening and disabling condition, especially for one that afflicts children. Nonetheless, we feel it can help give perspective when there are uncertainties about how well a model is capturing the health benefits of a treatment. This kind of analysis allows us to ask whether, even if the model were not capturing all the benefits that patients get from treatment, the price being charged could possibly be viewed as fairly scaled to its benefits. This is always a helpful way to "test" a model's judgment about fair pricing, but it's also particularly important to evaluate when there is limited or no competition, and insurers trying to negotiate over pricing can't walk away from the table because the treatment is a "must cover" kind of drug. Manufacturers in this situation have great discretion over the price they set, and if a manufacturer set the price for a cure of any condition at $100M or even $10M, we suspect that many patients and families would find the price excessive. The question then becomes what price reflects the top amount we can spend that would reward innovation and the good received by patients and their families who benefit from a treatment without doing ultimately more harm by the effects on insurance cost increases that force people to drop insurance or delay or forgo care. That's what this exercise in pricing analysis is meant to explore, and we hope you understand that our underlying motive is to push the limits of our model so that we can make sure we aren't potentially mislabeling a price as too high.***

4.	Societal and economic benefits should be included in ICER's cost-effectiveness model. The financial burden of CF is very high, both in direct medical costs and indirect costs, such as lost productivity and caregiving costs. Annual medical costs alone incurred by adult patients with severe CF can run upwards of $200,000 whereas younger patients with severe CF can incur even higher OOP costs. Direct medical costs do not even begin to capture the full financial burden of this disease. CF requires consistent care and caregiving, which places a huge emotional and financial burden on families. Very frequently when a child is diagnosed with CF, one parent will need to leave the workforce and become a full-time caregiver. CF patients also are very easily prone to infections and frequently require special accommodations in schooling and work. Several studies have shown that some of the largest costs of CF come from direct non-health care costs and indirect costs attributable to productivity losses. If ICER's goal is to truly capture the value of these treatments from a societal perspective, these costs must be included in the base case.	***We agree that CF is associated with substantial indirect costs. however, we have limited data on how the use of CFTR modulators may reduce those indirect costs. For example, do parents no longer need to leave the workforce to care for their CF child who is on a CFTR modulator? We did receive data on the impact of Kalydeco on employment status and incorporated that in our societal analysis. Still, this is an area that is in need of more data.***
5.	ICER fails to capture heterogeneity of the patient population. CF is a complex disease with considerable heterogeneity in both its severity and the degree to which therapies are effective. If ICER's aim is to produce actionable and accurate data for policymakers, then this heterogeneity must be incorporated in the model. Unfortunately, the ranges of the sensitivity analysis are the only tool within the report to convey the impact of this patient diversity, and ICER's choices for input ranges around its sensitivity analysis are unjustifiably narrow. The range for sensitivity in the analysis are just 0.002 – 0.005. This is an incredibly small variance given the choice for the base case is already very shallow. Additionally, given the heterogeneity, even within subgroups of CF patients, we believe it would be more appropriate to produce ranges, rather than means, for cost-effectiveness for a disease as diverse as CF. Averages are not consensus; they are just poor proxies for highly heterogeneous outcomes.	***The purpose of the sensitivity analysis is to evaluate uncertainty of the model parameters and not evaluate heterogeneity across individuals. It would not be appropriate to apply our analysis to individual patient decisions. The range cited reflects that of only one parameter that was subject to sensitivity analyses. Please see the report section on sensitivity analysis results for figures that include details of how widely the other parameters were varied.***

6.	ICER's decision not to model with dynamic pricing leads to consistently flawed assessments. ICER claims that it chooses not to incorporate the fact that drug prices change over time, as it would lead to a layer of uncertainty. However, it also states that numerous recently published models measuring the cost-effectiveness of cystic fibrosis drugs have indeed used dynamic pricing, suggesting ICER is willing to deviate from conventional methodologies often accepted by researchers and value assessors. The relevance of dynamic pricing is heightened in conditions where consequences accrue over an extended period of time. CF is an obvious example of this. In fact, the ICER model assumes treatment continues for up to fifty years. This is in stark contrast to many other interventions which are either evaluated over a short time period, or for which the consequences of intervention only accrue over a short period of time. Using static pricing in this context misunderstands how health care spending as well as uptake and integration of new technologies into health systems work. Uptake of new technologies does not happen overnight and does not begin at 100 percent utilization but rather happens slowly over time. When providing data for value attribution of a new technology within a living, evolving health system, the dynamic understanding of value is far more relevant than the static version. This point was made very clearly by Harvard researcher David Grabowski in a 2012 study of statins. Numerous studies have shown that using static prices in cost-effectiveness models make little sense when developing lifetime models. , , While it is not impossible, it is highly unlikely that the price of these drugs will be the same in ten or twenty years, let alone fifty. The price pattern for the vast majority of drugs is that of significant decline following 5-7 years of relative stability and on average results in prices close to 10-20% of launch price after ten years. This means that over the course of fifty years, relying on the launch price for the entire lifespan of each patient will likely overestimate costs between 300% and 400%.	***Consistent with best practice at international HTA agencies and with the great preponderance of academic work, ICER's cost-effectiveness analyses do not routinely make estimates of price changes across comparator treatments linked to patent and exclusivity time horizons, given the unpredictability of these changes in the US health care market. We also note that other prominent health technology assessment organizations, NICE and CADTH, criticized the inclusion of this assumption in the models submitted for their review.***

Patients for Affordable Drugs		
1.	The ICER value analysis is just one input that should be considered in arriving at the appropriate price for a new drug therapy. ICER does not address societal and ethical issues that are of utmost importance for the health and well-being of patients and our nation. ICER does not consider the role of the patient community, taxpayers and government in the invention of new drugs. Because ICER does not consider appropriate returns for the drug manufacturer, it cannot take into account societal investment which reduces risk for manufacturers and should therefore reduce return to the company commercializing the drug. ICER does not consider what is an appropriate price based on the investment to develop, produce, and distribute a drug. Given limited societal funds and necessary trade-offs when scarce resources are directed to unwarranted profits, this is an element that should be taken into account when arriving at a price.	***We agree that our report does not currently address the considerations raised in this comment. At our previous meeting, we discussed how investment and other support provided by the patient community and funding provided by the government and advocacy organizations substantially reduced the risk for the manufacturer, and noted that this should ideally be reflected in lower prices for these agents.***
2.	Cystic fibrosis patients who have encountered sudden insurance changes have been sued for the cost of their drugs. Patients on Medicaid caught in legal battles over drug costs in states like Arkansas have experienced sharp downturns in health . As ICER's latest draft report notes, some major insurers have created restrictive criteria in some cases, forcing patients of children with cystic fibrosis and adults with CF to spend hours of precious time engaged in onerous appeals processes.	***Thank you for these comments. We agree that it is inappropriate for insurers to implement inappropriately restrictive criteria that harms patient's well-being.***
3.	Trikafta's price should be lowered. Orkambi, Kalydeco, and Symdeko are priced too high according to ICER's analysis. Vertex's profitability and executive compensation merely confirm that fact looking at the issue through another lens. Vertex does not deserve a high risk adjusted price as philanthropy and taxpayer-funded research lowered the risk for the company dramatically. Vertex could use its tax windfall to lower drug prices, but it is instead paying executives and buying back stock. It can easily lower the price to come in line with ICER's findings.	***Thank you for these comments.***

Ryan Mincer		
1.	Change the way that you word your study conclusion so that you place a greater emphasis on quantitative quality-of-life data. The efficacy numbers for this drug speak for themselves. Trikafta is a good drug, an effective drug, and a relatively safe drug. I hope you can agree that quantitative quality-of-life data is an important and significant indicator of whether a drug is truly "cost-effective."	***We agree that there are substantive benefits with Trikafta in the short clinical trials and when projected out over a lifetime. The judgement about whether that is cost effective depends on the price relative to the substantial quality of life benefits and overall societal values. At the current price, Trikafta is not considered to meet common cost-effectiveness thresholds in the US or elsewhere in the world.***
Other		
Paul Langley		
1.	It appears that many people building simulated imaginary lifetime models (e.g., ICER Value Assessment Framework) believe that it is appropriate to consider the EQ-5D-3L (used in the cystic fibrosis model) as having ratio properties (i.e., a true zero). As this is incorrect would you explain why you persist? If you are unsure of the meaning of measurement scales, a full description of their mathematical properties is included in file:///C:/Users/Paul/Downloads/Working%20Paper%20No.%205%20March%202020.pdf You might also refer to the Bond and Cox reference on Rasch measurement theory.	***We (and most health economists) have the understanding that the EQ-5D (and other multi-attribute utility instruments) do have ratio properties. The EQ-5D value sets are based on time trade-off assessments (which are interval level), .***
2.	It has been recognized for almost 20 years that the EQ-5D-3L utilities are an ordinal manifest score as the basis for creating their utilities are responses on an ordinal scale for five symptom with three response levels for each symptom. If ICER believes this is not the case, in continuing to use the EQ-5D-3L, could ICER explain why they take this view? If you are unaware of this literature please consider the references below by Grimby et al, Tennant et al, McKenna et al (2 papers)	***We (and most health economists) have the understanding that the EQ-5D (and other multi-attribute utility instruments) do have interval-level 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 as an ordinal (ranked) scale.***
3.	If ICER rejects the notion of the EQ-5D-3L as an ordinal manifest score, could ICER demonstrate that, if we consider the interval measurement scale, that the EQ-5D-3L for the cystic fibrosis population has invariance of comparisons? Could ICER discuss this in the context of floor and ceiling effects? Is the utility difference between 0.4 and 0.45 equal to that between 0.8 and 0.85?	***The EQ-5D multi-attribute utility function is designed so that a utility difference of 0.05 is considered equivalent regardless of the starting point.***
4.	If ICER accepts that the EQ-5D-3L has interval properties and moves to ratio properties, can ICER demonstrate that the EQ-5D-3L has a 'true zero'? How would ICER reconcile this to the fact that with the EQ-5D-3L preference algorithm the lowest utility value allowed is -0.59? Would ICER agree that this invalidates the notion of a 'true zero'.	***ICER believes that the dead state represents a natural zero point on a scale of health-related quality of life. Negative utility values on the EQ-5D scale represent states considered worse than dead.***

5.	If ICER continues to apply the EQ-5D-3L in its models does the acceptance of the EQ-5D-3L with no 'true zero', i.e., a scale that allows (given distance from zero) multiplication and division, mean ICER accepts negative QALYs?	***See response above.***
6.	If ICER accepts the existence of negative QALYs for a disease state (i.e., EQ-5D-3L score < 1.0)) how does the ICER VAF factor this into lifetime QALYs?	***See response above.***
7.	ICER recognizes that the application of its value assessment framework rests on a belief that it is possible to create, within an imaginary lifetime model, claims expressed in terms of incremental costs per QALY for comparator products. If this is the case, how does ICER justify the creation of QALYs when it is demonstrably true that the EQ-5D-03L utilities fail to have ratio properties? In other words, you cannot multiply time spent in a disease state by an EQ-5D-3L score.	***See response above.***
8.	Given ICER's choice of utilities for constructing QALYs, could ICER demonstrate from one or more empirical assessments that the EQ-5D-3L has ratio fundamental measurement properties for the target cystic fibrosis hypothetical population in its reference case modeling?	***See response above. In addition, the EQ-5D is the most commonly-used health-related utility measure, and has been measured in cystic fibrosis patients and used in several prior analyses of cystic fibrosis treatments.***
9.	It is accepted in the social sciences and indeed in the physical sciences that measurement scales should have the property of unidimensional. That is, the focus should be on one attribute at a time. The EQ-5D-3L would appear to fail this standard in combining a number of health attributes into a single score? Would ICER agree or would ICER subscribe to the view that the EQ-5D-3L has demonstrable unidimensional properties? If so, could ICER demonstrate this for the target patient population?	***Please see the literature on multi-attribute utility theory.***
10.	If ICER cannot demonstrate that the EQ-5D-3L has ratio properties (let alone latent measurement properties) how can ICER persevere with its value assessment framework and recommendations for pricing and affordability? If the EQ-5D-3L algorithm allows for negative utilities (which it does) then this is conclusive that there is no 'true zero' and the notion of a QALY collapses because multiplication is disallowed.	***We disagree. Please see the responses above.***
11.	Is ICER prepared to argue that while the EQ-5D-3L fails the standards of fundamental measurement, this is immaterial in its construction of imaginary value assessment frameworks as they are only driven by assumption anyway?	***As stated above, we do not accept the premise of this question.***
12.	Is the reference case imaginary lifetime model intended to generate credible, evaluable and replicable claims for cost-effectiveness? If not, why not?	***Descriptive and predictive models are a mainstay of economic analyses, as well as most other scientific disciplines. We use transparent models that follow standard practices and are subjected to multiple scenario and sensitivity analyses.***

13.	How much credibility should be attached to the ICER model when it is only one of many that could create imaginary claims in cystic fibrosis for the products assessed? What sets the ICER model apart from others?	***We produce detailed reports describing the model's structure, assumptions, and inputs so that readers may judge the credibility of the model. At the draft report stage, we also share the actual model with relevant manufacturers for feedback and critique (the manufacturer of the treatments in this review declined to participate). In addition, we compare the model to prior published models in the same therapeutic area.***
14.	In the 2018 ISPOR task force report on health Economics (Neumann et al, Value Health 2018;21:119-25) it is determined that economic evaluations are intended, not to test hypotheses, but to inform decision makers of the approximate value of interventions in terms of imaginary incremental cost-per-QALYs gained. Does ICER subscribe to this view? How approximate is the modeled information in cystic fibrosis?	***ICER's value framework recognizes that decisions need to be made using evidence available at the time, no matter how approximate or uncertain. Our reports discuss in detail the variance and uncertainty around the available evidence for the clinical effectiveness of treatments. Our economic analyses explore uncertainty via scenario and sensitivity analyses, including probabilistic sensitivity analyses over plausible ranges of values.***
15.	In respect of 12 (above) how would ICER define the 'approximate value' of its cystic fibrosis modeling for incremental cost-per-QALY gains? How is this to be distinguished from 'approximate disinformation'?	***See response above.***
16.	Where different utilities and model structures are presented in cystic fibrosis lifetime modeled claims, how would ICER propose that their modeled 'approximate information' is more 'approximate' than other modeled claims for 'approximate information'?	***See responses above***
17.	Could ICER detail whether or not the EQ-5D-3L, as a health related quality of life measure, has a latent unidimensional construct? If not, how are we to characterize the 'construct' (if any) that supports this instrument?	***As above, please see the literature on multi-attribute utility theory.***
18.	It has been recognized since the 1960s (and in in health technology assessment since the 1990s) that if we are to capture the patient voice in therapy assessments, we require a needs based QoL instrument to capture therapy impacts with interval measurement properties. Why has ICER continued to apply generic measures of HRQoL defended by what many see as a bogus population perspective argument? Could ICER provide their case for non-patient centric HRQoL measures?	***The quality-of-life weights we used in calculating QALYs were derived from EQ-5D responses from CF patients in a prior published study. Appropriate data on HRQoL from the relevant clinical trials were not available. We encourage manufacturers and researchers to include disease-specific and generic measures of HRQoL/utility in future studies.***

19.	In the modeled case for cystic fibrosis ICER makes there is a clear case, based on fundamental measurement, to reject the modeled cost-per-QALY claims? Given ICERs persistence with this flawed methodology, why should we take these threshold cost-per-QALY claims and pricing recommendations seriously? How does ICER defend these recommendations?	***As outlined in the responses above, we disagree with the premise that the methodology is flawed.***
20.	Apart from the fatal measurement assumptions, ICER asks us to believe that is possible (even with the problematic EQ-5D-3L manifest score) that the claims for a range of outcome measures should be taken seriously? Is there any intent on ICER's behalf that these claims should meet the standards of normal science for credibility, evaluation and replication?	***As mentioned above, descriptive and predictive models such as this are a mainstay of economic analyses, as well as many other scientific disciplines.***