PIPC Partnership to Improve Patient Care

April 17, 2019

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

Dear Dr. Pearson:

The Partnership to Improve Patient Care (PIPC) is pleased to provide comments on the draft evidence report for *Treatment-Resistant Depression: Effectiveness and Value* from the Institute for Clinical Economic Review (ICER). We continue to urge ICER to move beyond QALYs and similar metrics, and to join others in the field in developing the next generation of value assessment models that are more patient-centered and consistent with our nation's drive toward personalized and precision medicine.

We provide the following concerns and suggestions related to ICER's draft report:

ICER disregards outcomes that matter to patients

As the National Alliance on Mental Illness (NAMI) highlighted in its November comment letter to ICER, individuals with treatment resistant depression (TRD) are in desperate need of treatments that offer fast, effective relief. The ICER model fails to capture the value of the treatment's immediate impact. For patients, the ability to quickly get back to work and their families is invaluable.

In addition to patients, clinicians have attested to the fact that one of the game-changing values of *esketamine* is this instantaneous effect. All other pharmaceutical options for depression are known to have a considerable lag time before their effectiveness kicks in; about 6-8 weeks. We also know the process of finding a 'fit' for a particular pharmaceutical treatment for a patient is largely trial and error and can be time-consuming and frustrating for both clinician and patient.

The ICER Markov model is constructed with each 'cycle' being three months long.
To appropriately evaluate the value of a new drug such as *esketamine*, which addresses a new patient-centered outcome, i.e. the speed of response to a serious and debilitating condition, ICER should move beyond a model limited to longer-term outcomes associated with traditional treatments. ICER should innovate and consider alternative models that are capable of capturing immediate outcomes in addition to longer-term outcomes.

Patients are anticipated to value and appreciate *esketamine*'s simplicity of delivery and immediacy of effect. The immediacy is of huge value to patients but is not captured in the Markov model, which values *esketamine's* immediate impact as equal to something that takes three weeks to work – a finding that is in direct contradiction with patients' preference for fast relief. In addition, *esketamine's* immediacy will have significant impacts on adherence and effectiveness, including for medications not related to a patient's major depressive disorder (MDD). That increased adherence and effectiveness will also decrease overall healthcare utilization.

Patients suffering TRD carry a severe disease burden, and the outcome that matters most to them based on a longitudinal wellness survey conducted by the Depression and Bipolar Support Alliance is, "to function as well as possible, especially in how they function at work, play, and with others." ICER fails to capture this outcome and instead continues to use the QALY, which is unable to capture essential patient preferences. As NAMI noted in its letter to ICER, the use of QALYs to measure treatments for mental illness is not appropriate, as these treatments are not disease-modifying in nature and devalue important outcomes for patients with depression.

ICER continues to produce value reports early - before adequate availability of evidence

We are concerned that this report continues a dangerous trend for ICER of conducting assessments of new drugs prior to the availability of sufficient evidence on their relative effectiveness compared to existing standards of care. We understand that ICER conducts its value assessments for use by payers, not as a tool to help patients make treatment decisions, yet its work has significant implications for patient access to care despite its lack of rigor. ICER's inflexibility on this issue is simplistic and inconsistent with the complex reality that has allowed patients in the U.S. to benefit from innovation early compared to other countries.[1]

- **Lack of consistency:** The information produced by ICER is not of a consistent quality or standard that would allow for a valid comparison to the standard of evidence used to value other treatment options for the same disease or condition.
- **Diminished quality of evidence:** Since 2015, there has been considerable variance in the quality of evidence in ICER assessments since receiving funding to expand its drug program in 2015, as witnessed by its evidence ratings tables. ICER's reviews of treatments in spinal muscular atrophy, multiple sclerosis and now treatment resistant depression rate in the moderate to low categories, including many marked as "promising but insufficient." Yet ICER's studies are often a reference for decisions related to coverage and access to care.

[1] Stevens W, Philipson TJ, Khan ZM, MacEwan JP, Linthicum MT, Goldman DP. Cancer mortality reductions were greatest among countries where cancer care spending rose the most, 1995–2007. Health affairs. 2015 Apr 1;34(4):562-70.

- **ICER does not update its review routinely as evidence improves:** ICER does not systematically update its models when new evidence on the effectiveness or cost of a new drug becomes available. In the one case where ICER did update a report, it was not as comprehensive as its initial report. Yet, there are there numerous examples of the effectiveness and cost-effectiveness of new drugs changing significantly as better evidence becomes available. Over time, real-world effectiveness data becomes more readily available, in particular with respect to longer term outcomes that may take years to generate.[2] There is a growing body of evidence that suggests that effectiveness is a dynamic, rather than a static measure. That is, relative or comparative effectiveness often changes over time as new technologies become embedded into practice; in essence as practitioners learn the best combinations of when, how, and to whom to treat to maximize the health benefit for individual patients.[3] Thankfully, clinicians do not blindly follow any one treatment pathway when they use new drugs. They combine their own experience of treatments with what they know from the existing evidence base. Clinicians also have far more complex patient groups than those seen in the RCTs from which ICER produces its effectiveness estimates for its models. Yet, ICER has not prioritized updates of its models to reflect real-world evidence.

The model does not accurately account for the cost burden of TRD

Depression is a devastating disease, which inflicts significant health and financial burden on our nation. Over 16 million adults experienced a major depressive incident in the past year, and mood disorders, including depression, are the third most common cause of hospitalization in the United States.[4] With this in mind, total economic cost of untreated depression should be taken into consideration, yet is not captured in the draft evidence report.

- **Non-drug cost data is misrepresentative:** The source of all non-drug cost data was from a single study undertaken almost 20 years ago. Although it has been inflated to 2018 prices, it's highly unlikely that the treatment patterns and sources of costs are the same 20 years later. There have been numerous more recent studies looking at U.S. costs in treatment resistant depression. In fact, a recent review of such studies published in 2014[5] compiled the results from 6 studies published since the study that was used by

[2] Grabowski DC, Lakdawalla DN, Goldman DP, Eber M, Liu LZ, Abdelgawad T, Kuznik A, Chernew ME, Philipson T. The large social value resulting from use of statins warrants steps to improve adherence and broaden treatment. Health affairs. 2012 Oct 1;31(10):2276-85.
[3] Incerti, D., et al. "An Empirical Analysis of The Role of Learning by Doing in Dynamic Cost-Effectiveness." *Value in Health* 20.9 (2017): A435-A436.
[4] National Alliance on Mental Illness. Mental Health by the Numbers. Available at: https://www.nami.org/Learn-More/Mental-Health-By-the-Numbers
[5] Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996–2013. Psychiatric services. 2014 Aug;65(8):977-87.

ICER, suggesting that the cost of TRD was between 30-100% higher on average than treatment *responsive* depression.

- **Cost of comorbidities was not captured:** The report did not measure the impact of improved treatment effect on costs beyond those associated with the primary condition. MDD has been strongly associated with opioid abuse over the last decade, a current public health epidemic in the United States which would not be captured in the 2002 study ICER uses. A simple inflation rate cannot account for changes in how diseases are addressed culturally, new emerging trends, or how conditions influence and are influenced by other co-morbid conditions over time.

Reports capturing value to the patient require timely and relevant data related to a holistic set of costs experienced by patients. Additionally, models must recognize the complex nature of conditions that are associated with high sets of comorbidities, such as TRD. At each stage of progression, the burden and cost of treatment of these conditions rises, and models should reflect the burden on patients in particular.

Mortality estimates used are misleading

The mortality multipliers in the draft evidence report may underestimate the true mortality associated with TRD. ICER referenced a particular study to calculate the mortality multipliers for TRD in the model (Ruetfors 2018)[6] that compared the mortality rate of a TRD population to a population suffering treatment-susceptible depression, as opposed to comparing to the mortality rate of the general population. Yet, the ICER model applies the TRD multipliers to general population mortality rates (the US Human mortality database).[7] This makes the assumption that people suffering treatment-susceptible depression have the same mortality rates as the general population, an assumption that runs counter to available evidence.[8] Also, the definition of TRD in this study was more ambiguous, and less severe than the definition of TRD used in the model for triggering the use of *esketamine*, which is another difference that may underestimate the true mortality associated with untreated TRD.

In conclusion

Thank you for your consideration of PIPC's comments. With over 4 million adults suffering from TRD and limited treatment options, it is seminally important that ICER incorporate patient's needs and preferences into its analysis. We again call upon ICER to consider innovating its

[6] Reutfors J, Andersson TM, Brenner P, Brandt L, DiBernardo A, Li G, Hägg D, Wingård L, Bodén R. Mortality in treatment-resistant unipolar depression: A register-based cohort study in Sweden. Journal of Affective Disorders. 2018 Oct 1;238:674-9.

[7] Human Mortality Database. 2016. www.mortality.org. Accessed February 2, 2019

[8] Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA psychiatry. 2015 Apr 1;72(4):334-41.

model to better recognize the considerations that matter most to patients when making treatment decisions instead of using metrics such as QALYs and the evLYG that present an impossible choice between discrimination and inadequate consideration of patient-centered outcomes.

Sincerely,

Tony Coelho
Chairman, Partnership to Improve Patient Care