PIPC Partnership to Improve Patient Care

December 22, 2023

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

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment of KarXT for schizophrenia.

Schizophrenia is a rare and serious mental disease that impacts how a person thinks, feels, and behaves. It can be an incredibly challenging disease for the person living with it as well as their caregivers, and, if not well controlled, it can impact an individual's ability to work and live independently. As ICER conducts its assessment of treatments for schizophrenia, PIPC urges it to consider the following comments.

The EQ-5D is an inappropriate PRO tool to use in this assessment as it is insensitive to changes in QOL in mental health.

The generic EQ-5D is a tool known to be insensitive to changes in quality of life (QOL) for psychiatric conditions. In general, generic preference-based measures do not correlate well with symptoms for psychiatric conditions or with clinician-assessed outcomes. This can be challenging for economic evaluation since interventions typically target positive symptom reduction that would be missed by measures such as the EQ–5D.[1] A specific example of this is a study of chronic schizophrenia using measures of psychopathology and functioning to establish change in which the EQ–5D did not have a significant correlation with negative symptoms, disorganization, depression, excitement and general symptoms.[2] These points have also been found in subsequent studies on the use of generic preference based measures in most areas of mental health.[3]

As a general rule, disease specific tools, are stronger and do a better job reporting true patient outcomes. PIPC would recommend these always be used over the EQ-5D, but for this assessment specifically, the EQ-5D is a particularly poor choice.

ICER's assessment presents a dangerous oversimplification of a complex disease.

[1] Saarni SI, Härkänen T, Sintonen H, Suvisaari J, Koskinen S, Aromaa A, Lönnqvist J. The impact of 29 chronic conditions on health-related quality of life: a general population survey in Finland using 15D and EQ-5D. Quality of life Research. 2006 Oct;15:1403-14.
[2] van de Willige, G, Wiersma, D, Nienhuis, FJ, Jenner, JA. Changes in quality of life in chronic psychiatric patients: a comparison between EQ-5D and WHOQoL. Qual Life Res 2005; 14: 441–51
[3] Brazier J. Is the EQ–5D fit for purpose in mental health?. The British Journal of Psychiatry. 2010 Nov;197(5):348-9.

ICER chooses to drastically simplify the disease by over-categorizing many health states into only two – with and without severe symptoms. There are many problems with over-categorizing of diseases by using too few health states, which PIPC has pointed out to ICER in the past. If ICER's actual goal is to show true efficacy of a treatment, this practice hinders that goal. If a treatment is represented by movement of patients from a worse state to a better state, if the number of states is small – or classification too crude - the number of people transitioning between states may result in an underestimate of the true effect of the treatment. Doing so tends to rely on the assumption of a similar distribution of severity within states as the distribution of severity across states. This over-categorization of outcomes has been shown to lead to underestimation of treatment effects.[4,5]

ICER's modified societal perspective calculations seem to rely on illogical assumptions.

Before getting into the weeds on this topic, it should be noted that ICER should always, particularly in the case of a disease with deep societal implications like schizophrenia, be using the societal perspective as its base case versus the health care perspective.

In ICER's draft assessment, it chose to use a health care perspective as its base case and then presented a modified societal perspective. The report suggests that the modified societal perspective estimates of cost-effectiveness of KarXT are close to identical to that of the base-case. The argument for this is that the "*the cost savings resulting from productivity gains and fewer criminal justice encounters [are] being offset by additional time required of the caregiver*." This is illogical, as the source of any reduction in criminal costs and increase in productivity would be a patient spending more time in milder disease states, which would also indicate lower caregiver needs. This inconsistency calls into question the validity of ICER's data, and PIPC would urge ICER to work more closely with the patient groups representing individuals with schizophrenia to understand more clearly the burden of disease as well as the societal and caregiver impact.

ICER must move away from the assumption that all patients are average.

ICER continues to conduct its assessments to show benefit to the "average" patient. Ultimately this does not provide valid information to help inform decision making in a way that provides high quality patient care. A population average is not a proxy measure that represents all patients. An average doesn't represent all patients – even as a proxy. An average patient acts as a proxy solely for a handful of patients who happen to land in the middle of a random distribution of patients. These patients are not the majority, they aren't the most needy, and they aren't even those for whom the intervention itself would necessarily be most effective.

If ICER wishes to provide helpful information with the aim of informing a decision-maker as to what value a new therapy might have for any patients, it should focus on producing an estimate – or a range of estimates - for as many of that wide range of patients, or patient types, as is possible. It is well

[4] Altman DG, Royston P. The cost of dichotomising continuous variables. Bmj. 2006 May 4;332(7549):1080.
[5] Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Statistics in medicine. 2006 Jan 15;25(1):127-41.

established that generating and reporting of differential value assessment estimates across subgroups leads to substantial health gains, both through treatment selection and coverage.[6,7]

Conclusion

PIPC urges ICER to reconsider some of its modeling choices to ensure it is providing an accurate picture of value to the patient and society.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

[6] Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered health care. Journal of health economics. 2011 May 1;30(3):549-59.
[7] Espinoza MA, Manca A, Claxton K, Sculpher MJ. The value of heterogeneity for cost-effectiveness subgroup analysis: conceptual framework and application. Medical Decision Making. 2014 Nov;34(8):951-64.