

December 6, 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) appreciates this opportunity to comment on the Institute for Clinical and Economic Review (ICER) study of treatments for Acute Migraine. Migraine is a particularly debilitating disease with huge physical, emotional, and economic costs. Migraine is the sixth most disabling illness in the world and healthcare and lost productivity costs associated with migraine are estimated to be as high as \$36 billion annually in the United States.¹ In addition to this huge physical and financial burden, at this point, there are currently limited effective treatments, so it is important that new treatments are assessed responsibly and with a patient-centered lens.

We would like to echo The Headache & Migraine Policy Forum's comments on the draft scoping document and request you consider renaming the assessment to properly reflect the included content: "Innovative Acute Treatments for Migraine Attacks."

The QALY is Flawed

PIPC would like to reiterate our concern with ICER's use of the QALY. As we have noted in several past comment letters, the QALY is not an appropriate methodology for use in value assessments, particularly where the patient population is very heterogenous, as in migraine. The Headache and Migraine Policy Forum also touches on this heterogeneity in their report noting that the experience of migraine exists on a spectrum more than other chronic disease. It is also important to note that a recent review suggested that generic PROs have been shown to have less reliability and validity than disease-specific PROs in migraine evaluation such as HIT-6, MSQv2.1 and the PPMQ-R.²

The QALY is also widely acknowledged to discriminate against those with disabilities and chronic illnesses. In fact, they have long been precluded from use in public health programs for this very reason. The QALY is not an appropriate metric to use when evaluating treatments for a chronic condition that is the sixth leading cause of disability. Migraine is considered an invisible disability with an impact on quality of life that may not be appreciated by the general population.

¹ The Migraine Resource Foundation. Migraine Facts. Accessed November 19, 2019.

² Haywood KL, Mars TS, Potter R, Patel S, Matharu M, Underwood M. Assessing the impact of headaches and the outcomes of treatment: a systematic review of patient-reported outcome measures (PROMs). *Cephalalgia*. 2018 Jun;38(7):1374-86.

The Draft Evidence Report Makes the Oversimplified Assumption That There are No Mortality Effects in Migraine Treatment.

The ICER Report makes a statement that it assumes there are no mortality effects in migraine treatment. This is a simplistic assumption, as a number of studies have shown people with more severe types of migraine (with aura for example) have higher rates of all-cause mortality in both men and women.³ Studies have also shown higher rates of both suicide and suicidal ideation in migraine patients⁴, and more broadly in patients suffering with conditions that include chronic pain.^{5,6} Considering this research, assuming a therapy that successfully reduces the pain burden for migraine patients will have no effect on mortality does not capture the full picture.

Most studies that look at migraine and mortality differentiate specifically between migraine with aura (strong mortality effect) and migraine without aura (weak),^{7,8} reiterating the importance of the risk of dilution of effect by inadequate diagnosis or subgroups analysis by severity. In all it was estimated on average that people with migraine with aura had mortality rates between 10-20% higher than a matched cohort of people without the condition. In a scenario like this, in which the risk of mortality is higher in a particular disease state, the potential expected impact of successful therapy would be reduced risk. Even if mortality isn't an outcome in trials of migraine therapy, drawing the line between successful treatment and reduced mortality should at least be discussed and not simply assumed as null.

ICER Makes No Attempt to Incorporate Quality of Life Gains from Reduced Anxiety Around Migraine Attacks.

Studies have shown that HRQOL is lower for migraine patients 'between' attacks as well as during attacks as a direct result of the anxiety anticipating an attack.⁹ In one study compared with control subjects, "migraineurs perceived more symptoms and greater emotional distress as well as disturbed contentment, vitality and sleep."¹⁰ Another showed that "Compared with non-

³ Gudmundsson LS, Scher AI, Aspelund T, Eliasson JH, Johannsson M, Thorgeirsson G, Launer L, Gudnason V. Migraine with aura and risk of cardiovascular and all cause mortality in men and women: prospective cohort study. *Bmj*. 2010 Aug 24;341:c3966.

⁴ Breslau N. Migraine, suicidal ideation, and suicide attempts. *Neurology*. 1992 Feb 1;42(2):392-.

⁵ Hassett AL, Aquino JK, Ilgen MA. The risk of suicide mortality in chronic pain patients. *Current pain and headache reports*. 2014 Aug 1;18(8):436.

⁶ Pompili M, Di Cosimo D, Innamorati M, Lester D, Tatarelli R, Martelletti P. Psychiatric comorbidity in patients with chronic daily headache and migraine: a selective overview including personality traits and suicide risk. *The journal of headache and pain*. 2009 Aug;10(4):283.

⁷ Liew G, Wang JJ, Mitchell P. Migraine and coronary heart disease mortality: a prospective cohort study. *Cephalalgia*. 2007 Apr;27(4):368-71.

⁸ Schürks M, Rist PM, Shapiro RE, Kurth T. Migraine and mortality: a systematic review and meta-analysis. *Cephalalgia*. 2011 Sep;31(12):1301-14.

⁹ Wacogne C, Lacoste JP, Guilibert E, Hugues FC, Le Jeune C. Stress, anxiety, depression and migraine. *Cephalalgia*. 2003 Jul;23(6):451-5.

¹⁰ Dahlöf CG, Dimenäs E. Migraine patients experience poorer subjective well-being/quality of life even between attacks. *Cephalalgia*. 1995 Feb;15(1):31-6.

migraineurs and to others with chronic conditions, migraineurs report compromised physical, mental, and social functioning, particularly those with a high frequency of attack.”¹¹

Many patients shared with ICER that this constant anxiety caused them to have lower quality of life even when they were not having a migraine attack. ICER acknowledged this in their “Insights Gained from Discussions with Patients and Patient Groups” section of the report yet made no attempt in the actual model to incorporate the quality of life gains from reduced anxiety that comes from having improved options for episodic treatment. As such the construction of the ICER model, which only includes the estimation of QALY gains ‘within’ each acute attack, will inevitably be an underestimate of the overall effect of any therapy as it excludes those gains that are experienced outside acute attacks.

This highlights our consistent concern that ICER seeks patient input but fails to give it real credence by incorporating it into the actual model.

ICER Continues to Use Third-Party Health Utility Estimates, which Underestimate the Effect of Treatment.

ICER continues to use third-party health utility estimates and apply them to the health states used to construct the QALY estimates rather than using health-related quality of life (HRQOL) data directly from the RCTs themselves to calculate the utilities in its QALY calculations. It has been shown that this over-translation, or categorization, of outcomes into utility sets by health state categories rather than from direct sources underestimates the effects of therapies.¹² Using a translated utility from a third source as a proxy leads to an oversimplification of health states. This limits our full understanding of the effects of any therapies under investigation and can lead to them being shown to be less effective based on faulty data. We encourage ICER to cease using this type of third-party health utility estimate.

We also share the concerns of others that ICER is using clinical studies that are 25 years old and comparing them to more recent studies. Yet, we know today that the placebo response has changed over time. ICER’s model cannot be accurate when ICER’s literature review that underlies the cost effectiveness model relies on this 25 year old data instead of real-world data that better reflects the patient experience.

ICER’s Model has Inherent Flaws

When designing and executing a cost-effectiveness model, it can very quickly become a box-checking exercise: produce a Markov model that is constructed around the main outcome

¹¹ Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: the GEM study. *Neurology*. 2000 Sep 12;55(5):624-9.

¹² Altman DG, Royston P. The cost of dichotomising continuous variables. *Bmj*. 2006 May 4;332(7549):1080; Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Statistics in medicine*. 2006;25(1):127-41.

measures; get sources for drug cost, utilities and transitions; chose a timescale; make assumptions where data is missing; etc. This becomes quickly reductive and therefore inaccurate due to its inability to capture the real-world patient experience with the particular disease and the value of treatment.

While there are undoubtedly numerous inputs that are ‘correct’ in the ICER migraine model, it also contains structural flaws. Ultimately, the real test is whether it works, and, in many ways, this model is inconsistent with common sense based on the facts. We know migraine is a condition impacting a group of people who experience unpredictable attacks of severe pain on a minimum of a weekly basis (mean 4.8 attacks per month) which ICER’s states, “*can be a disabling, chronic condition that can impact all aspects of life including personal relationships and ability to work.*” The drugs under consideration are more effective than standard of care by orders of magnitude of 2-5 times (tables 3.3-3.7). The drugs in question are assumed in the model to cost \$70.

Relying on this basic set of facts, it does not meet common sense standards that the model results would find these therapies to not be cost-effective. Nor it is transparent how the aforementioned results were derived because ICER still does not publish its models or make them open source. From what we can surmise, the most significant issues seem to lie in the narrow scope of the model. Our best guess is that the underlying factor leading to this conclusion is based on how quality of life was incorporated or the source of that information. One alternative would have moderate migraine down from 0.79 to 0.53 and severe migraine down from 0.44 down to -0.20.¹³ It is not clear why the chosen source of quality of life data is selected over others, or even that others are not used as part of a sensitivity analysis.

Another factor for this conclusion may be the measure of the impact of reducing migraines and their severity as limited to the length of the individual attacks rather than across the entire period for the patient. This would be an oversimplification of the model that goes too far from the day-to-day reality of the disease for most patients.

We would suggest a thorough review of the construct of the model and a detailed review by migraine patients themselves on how it represents the real patient experience.

Conclusion

ICER continues to overlook outcomes that matter to patients in favor of overly simplistic QALY-based models. We urge ICER to be more thoughtful in its model construction and take seriously the feedback from patients and clinicians who are experts in migraine attacks.

¹³ Stafford MR, Hareendran A, Ng-Mak DS, Insinga RP, Xu R, Stull DE. EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of migraineurs. Health and quality of life outcomes. 2012 Dec;10(1):65

Sincerely,



Coelho

Tony Coelho

Chairman, Partnership to Improve Patient Care