PIPC Partnership to Improve Patient Care

May 9, 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 gene therapies for Sickle Cell Disease (SCD).

SCD is an incredibly challenging disease that disproportionately affects Black Americans. Following a historic lack of investment, in recent years some innovators have turned their attention to developing treatments and, now, gene therapies for SCD. PIPC followed and commented on ICER's 2020 assessment of treatments for SCD and have noticed ICER is still incorporating some of the flaws we and others pointed out in 2020, including continued use of the Quality-Adjusted Life Year (QALY), a failure to acknowledge that standard of care is often not standardized, and failure to adequately incorporate pain and other concerns like fatigue into its model.

PIPC encourages ICER to consider the following comments.

QALYs are an inappropriate metric for use.

PIPC has consistently urged ICER to abandon the use of the discriminatory QALY. Given the complex nature of SCD, its severity, and the fact that the burden falls onto specific groups within society, the QALY is a particularly inappropriate method for evaluating interventions aimed at its alleviation.[1] Numerous studies have highlighted that factors such as severity of disease,[2] pain levels, and sparse availability and limited effectiveness of alternative treatments should be considered key determinants of needing higher priority in healthcare settings.[3,4] A number of health technology assessment systems in Europe countries such as Norway, Sweden and the Netherlands[5] actively use information on these factors to inform approval decisions for new medicines, due to the limitations and simplicity of the QALY as a measure of health gain.

[1] Levenson JL, McClish DK, Dahman BA, Bovbjerg VE, Citero VD, Penberthy LT, Aisiku IP, Roberts JD, Roseff SD, Smith WR. Depression and anxiety in adults with sickle cell disease: the PiSCES project. Psychosomatic medicine. 2008 Feb 1;70(2):192-6.
[2] Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health Economics. 1999;8:25–39
[3] McKie J, Richardson J. Social preferences for prioritizing the treatment of severely ill patients: the relevance of severity, expected benefit, past health and lifetime health. Health Policy. 2017 Aug 1;121(8):913-22
[4] Gu Y, Lancsar E, Ghijben P, Butler JR, Donaldson C. Attributes and weights in health care priority setting: a systematic review of what counts and to what extent. Social Science & Medicine. 2015 Dec 1;146:41-52.
[5] Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. The European Journal of Health Economics. 2018 Jan 1;19(1):123-52.

ICER should prioritize the incorporation of heterogeneity of patients, both in terms of how they experience the disease, but also in terms of pure population group heterogeneity and the functional difference in access to and quality of the healthcare available to them. Ignoring this reality makes the results of the report difficult to interpret and potentially meaningless to guide what types of care should and shouldn't receive investment within the healthcare system.

When evaluating gene therapies or other "one-time" treatments that target chronic, progressive conditions, more care should be applied to capturing the benefit of limiting the burden of accessing regular care.

For patients with SCD, access to high-quality care can be challenging and for many patients out of reach. One of the potential value-adds of gene therapies is their use could ultimately reduce the burden on patients of poor health care access and delivery. Diseases that have the most limited current standard of care, or diseases where patients have suffered most from limited access to high quality care, is where the marginal value of gene therapies are likely to be highest. Whereas the ICER model expresses the marginal benefit between successful treatment of the disease with gene therapy and the optimum standard of care, which is unlikely to be experienced by the vast majority of SCD patients.

The ICER report itself states that patients commonly receive care from generalists, emergency nurses, and hospitalists who may not be equipped to help them manage their disease.[6,7] It also acknowledges that there are not enough doctors and other medical providers who are adequately trained in the management of SCD, particularly for adults. A national survey of over 3,000 family physicians revealed that only 20% of respondents felt comfortable treating SCD.[2,8] There is evidence of preventable deaths and irreversible damage that result from long wait times in the emergency room as well as the increased mortality from events that occur in the hospital. This is unlikely to have been the level of care represented in RCTs for the comparison arm, and so already marginal differences are underestimated. It would be more helpful to express a wider set of potential comparators than a 'standardized' alternate standard of care. While technically correct, the relative comparison described and reported by ICER is unlikely to be relevant to the majority of SCD patients. This approach not only ignores problems of access to standard treatments, but as a result underestimates the relative value of a one-off treatment for SCD, that bypasses the bulk of the limitations of the healthcare systems that SCD patients have been very clear about to ICER during both this assessment and its previous SCD assessment.

[6] Lee L, Smith-Whitley K, Banks S, Puckrein G. Reducing Health Care Disparities in Sickle Cell Disease: A Review. *Public Health Rep.* 2019;134(6):599-607
[7] Mainous AG, 3rd, Tanner RJ, Harle CA, Baker R, Shokar NK, Hulihan MM. Attitudes toward Management of Sickle Cell Disease and Its Complications: A National Survey of Academic Family Physicians. *Anemia.* 2015;2015:853835
[8] Begley S S. 'Every time it's a battle': In excruciating pain, sickle cell patients are shunted aside. https://www.statnews.com/2017/09/18/sickle-cell-pain-treatment/. Published 2017. Accessed 21 April 2023.

ICER's model underestimates incidence and costs associated with vaso-occlusive crises (VOCs)

The model uses Baldwin[9] as a source for the cost of VOCs. This paper is a systematic literature review. Within this review, the paper highlights marginal costs associated with a VOC, as ranging from $4,609 taken from Shah (2020a)[10] to $45,515, taken from Shah (2020b).[11] It is not clear why the ICER model just uses the number at the bottom of the range. It would be a more accurate representation to acknowledge the full range of potential costs associated with VOCs.

Similarly, the mean number of VOCs per year is listed as 4 with no source, as it is merely assumed. Assuming this value is concerning as it is one of the main drivers of cost-effectiveness in the model. In reality, the number of VOCs per year is highly variable, and, because of this, the potential value of successful treatment may vary considerably by severity of disease. The only systematic study collating all published research on the frequency of VOCs is Zaidi et al (2021),[12] which highlights this point. It concludes, from 52 studies, that although highly variable the proportion of patients experiencing ≥ 5 VOCs per year ranged from 18 to 59%. Despite this body of research, the range of VOCs presented in ICER's assessment is between 2 and 6, so it is likely that many patients are excluded from this sample.

ICER ignores the role of heterogeneity in severity of pain in estimating utilities, which is likely to underestimate the overall value of effective treatments in SCD.

Disease burden in SCD comes primarily from pain. Pain management has for many years been a primary part of disease management for SCD patients, and most SCD patients rank pain as being the most difficult part of having the disease.[13] It is also a large driver in differences in quality of life (and health utility) when determining the relative value of different treatments for SCD, but it has been largely ignored in the ICER model. SCD patients experience pain that is poorly understood and often poorly treated. Adult patients may face barriers to comprehensive SCD care and stigmatization of their care-seeking behavior by providers, forcing them into maladaptive coping strategies.[14]

A better attempt at addressing the role of pain in this exercise is necessary to fully comprehend the impact of its alleviation for sickle cell disease patients.

---

[9] Baldwin Z, Jiao B, Basu A, Roth J, Bender MA, Elsisi Z, Johnson KM, Cousin E, Ramsey SD, Devine B. Medical and non-medical costs of sickle cell disease and treatments from a US perspective: a systematic review and landscape analysis. PharmacoEconomics-Open. 2022 Jul;6(4):469-81.

[10] Shah N, Bhor M, Xie L, Paulose J, Yuce H. Medical resource use and costs of treating sickle cell-related vaso-occlusive crisis episodes: a retrospective claims study. J Health Econ Outcomes Res. 2020;7(1):52–60

[11] Shah NR, Bhor M, Latremouille-Viau D, Kumar Sharma V, Puckrein GA, Gagnon-Sanschagrin P, et al. Vaso-occlusive crises and costs of sickle cell disease in patients with commercial, Medicaid, and Medicare insurance—the perspective of private and public payers. J Med Econ. 2020;23(11):1345–55

[12] Zaidi AU, Glaros AK, Lee S, Wang T, Bhojwani R, Morris E, Donohue B, Paulose J, Iorga ŞR, Nellesen D. A systematic literature review of frequency of vaso-occlusive crises in sickle cell disease. Orphanet Journal of Rare Diseases. 2021 Dec;16:1-2.

[13] McClish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL, Roseff SD, Smith WR. Health related quality of life in sickle cell patients: the PiSCES project. Health and quality of life outcomes. 2005 Dec;3(1):1-7.

[14] Smith, W.R., Bovbjerg, V.E., Penberthy, L.T., McClish, D.K., Levenson, J.L., Roberts, J.D., Gil, K., Roseff, S.D. and Aisiku, I.P., 2005. Understanding pain and improving management of sickle cell disease: the PiSCES study. *Journal of the National Medical association*, *97*(2), p.183.

PIPC Partnership to Improve Patient Care

Conclusion
PIPC urges ICER to reconsider the use of the QALY and ensure it is using accurate and representative inputs in its model.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care