PIPC Partnership to Improve Patient Care

August 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 treatments for Metachromatic Leukodystrophy (*MLD*).

MLD is a rare hereditary disease for which there is no cure and very limited options for supportive care. MLD is a devastating disease, which leads to progressive nerve damage throughout the body and brain, eventually leading to early death for patients. Treatments for this rare disease are urgently needed, and it is imperative that ICER consider the rare patient population and severity of the disease in its assessment.

QALYs are discriminatory and should not be used in value assessment.

Multiple studies have shown that cost-effectiveness models that use the quality-adjusted life year (QALY) discriminate against patients with chronic conditions[1] and people with disabilities.[2] There is widespread recognition that the use of the QALY is discriminatory. The QALY has historically been opposed by the American public and policy makers. The National Council on Disability (NCD), an independent federal agency, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.[3]

Traditional cost utility methods, like those ICER uses, often serve to undervalue treatments for highly severe illnesses. As a result, such studies may lead payers to underpay for treatment of severe illnesses, like MLD. ICER should be evolving away from use of the QALY, and, instead, measuring value based on the most up to date science and improved health utilities reflecting the value to the patient.[4]

ICER should practice severity weighting, as is accepted by many other HTA bodies.

[1] Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.
[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 Feb;8(1):25-39.
[3] https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf
[4] MacKillop E, Sheard S. Quantifying life: understanding the history of quality-adjusted life-years (QALYs). Social Science & Medicine. 2018 Aug 1;211:359-66.

As PIPC has stated in past comments to ICER, it is imperative that it follow the model of other HTA organizations and incorporate severity weighting in its assessments. Non-linear utility function in cost-utility analysis has been widely accepted with the discipline of health economics and has been incorporated into value assessment methods globally. European countries such as Norway, Sweden, the Netherlands,[5] and most recently the UK's NICE,[6] are actively using information on severity of the disease in the question to better inform approval decisions for new medicines. These countries are addressing the problem by developing multiple thresholds specific to each disease.

MLD is a devastating disease, and based on the utilities ICER chooses to use in its model, most other HTA bodies would consider it a severe condition and adjust their thresholds. In the Netherlands it would be granted a threshold four times that used for less severe conditions.[7] In Norway it would be granted a threshold of three times that for less severe conditions.[8] PIPC urges ICER to familiarize itself with the latest developments in value assessment instead of remaining wedded to a traditional CEA, which is dated in many ways. This will enable ICER to conduct more accurate, sensitive assessments for patients.

ICER continues to conduct premature assessments.

Once again, ICER is choosing to conduct this assessment at an early stage of our understanding of the treatment in question without all of the information available. Within this construct, ICER chooses to make overly conservative assumptions about the long-term value of the treatment in question and its impact on a specific set of outcomes. This type of premature and conservative assessment can be harmful to patients, painting a distorted picture of the relative value of a new technology.

ICER's premature assessment also leads it to raise questions about the durability of the treatment. Questions of durability of treatment of any new technology are common, but these should not be used to restrict access to patients who will benefit today. ICER states that long-term durability is unknown for arsa-cel in MLD, but there is up to 11 years of follow-up data in the LI-MLD patients[9] and up to 9 years in the EJ-MLD patients.[10] In both cases the Kaplan-Meier curves suggest quite considerable evidence for durability. It leaves us with the question as to what exactly is 'enough' evidence of durability in a novel drug that can reduce mortality by over 60% over ten years. The most problematic aspect of ICER's commentary on durability is that this reasoning assumes there is no downside to delaying access to new therapies, but this is far from true for patients waiting for treatments, especially those with few, if any, options. Every year this drug is not available for LI-MLD and EJ-MLD treatment, patient lives are

[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.
[6] Collins C, Cheng J, Taylor I, Mumford A. HTA73 Evaluation of NICE Severity Modifiers. Value in Health. 2022 Dec 1;25(12):S310.
[7] Reckers-Droog V, van Exel J, BrouwerW. Equity weights for priority setting in healthcare: severity, age, or both? Value Health. 2019;22(12):1441–1449.
[8] Magnussen J, Aaserud M, Granaas T, et al. På ramme alvor - Alvorlighet og prioritering. Government of Norway. https://www.regjeringen.no/contentassets/d5da48ca5d1a4b128c72fc5daa3b4fd8/summary_the_magnussen_report_on_severity.pdf.
[9] Orchard Therapeutics. A Safety and Efficacy Study of Cryopreserved OTL-200 for Treatment of Metachromatic Leukodystrophy (MLD). Orchard Therapeutics. Clinicaltrials.gov Web site. https://classic.clinicaltrials.gov/ct2/show/NCT03392987. Published 2022. Accessed2023.
[10] Fumagalli F, Calbi V, De Mattia F, et al. Long-term clinical outcomes of atidarsagene autotemcel (autologous hematopoietic stem cell gene therapy for metachromatic leukodystrophy) with up to 11 years follow-up. The San Raffaele Telethon Institute For Gene Therapy. 2023.

lost. Patient lives should not be ignored in order to suit a conservative view of what constitutes enough evidence.[11]

ICER should use the societal perspective as the sole base case in this model.

MLD has an immense societal impact, including caregiver burden. Ignoring this reality has the potential to significantly exacerbate inequality within the disease state. The reality is that, given the immense caregiving needs of MLD, families are forced to make very difficult choices. Either the child's care and/or the family's earning potential may be compromised as a result. ICER has chosen to give equal weight to its healthcare perspective results that exclude caregiver utilities and indirect costs, which we believe is a mistake. For some diseases the burden on caregivers and the impact on social care costs make the societal perspective a more relevant choice than the health care perspective. NICE, which ICER leans heavily on for its approach to value assessment, has already included caregiver utility in its cost-effectiveness models for diseases such as Alzheimer's, MS and Parkinson's disease.[12] It is also the recommended perspective for cost-effectiveness models of the 2nd panel on cost-effectiveness[13], and ISPOR.[14]

In addition, the source for the caregiver dis-utilities were from a source that evaluated a different disease, neuronal ceroid lipofuscinosis type 2,[15] and they show no gradation from GMFC health state 2 to GMFC health state 6. This is not an accurate source for these utilities as the level of care required, and the resulting impact on a caregivers' quality of life across these states of disease would be considerably different. ICER shares in the assessment that it was given a set of caregiver utilities directly by the manufacturer that does indeed vary by GMFC state. PIPC would recommend using that source for caregiver utilities.

ICER should factor system effects into its assessment.

The availability of a treatment for MLD changes the diagnostic and screening landscape for the disease. It means that patients are more likely to find an effective treatment, but it also triggers system effects.[16] In other words, the existence of the treatment leads to patients (and parents) having access to diagnostic certainty at an early stage of disease, cutting out the significant pathways of misdiagnosis and harmful and ineffective treatment strategies which can worsen the feelings of helplessness, anxiety and stress for

[11] Stevens W, Philipson T, Wu Y, Chen C, Lakdawalla D. A cost-benefit analysis of using evidence of effectiveness in terms of progression free survival in making reimbursement decisions on new cancer therapies. InForum for Health Economics and Policy. 2014 Jan 1, 17(1);21-52.
[12] Afentou N, Jarl J, Gerdtham UG, Saha S. Economic evaluation of interventions in Parkinson's disease: a systematic literature review. Movement disorders clinical practice. 2019 Apr;6(4):282-90.
[13] Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. Jama. 2016 Sep 13;316(10):1093-103.
[14] Garrison Jr LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ispor drug cost task force report—Part II. Value in Health. 2010 Jan;13(1):8-13.
[15] National Institute for Health and Care Excellence. Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2. https://www.nice.org.uk/guidance/hst12. Published 2019. Accessed August 1, 2023
[16] Jena AB, Stevens W, Gonzalez YS, Marx SE, Juday T, Lakdawalla DN, Philipson TJ. The wider public health value of HCV treatment accrued by liver transplant recipients. The American journal of managed care. 2016 May;22(6 Spec No.):SP212-9.

patient and family. These effects are not incorporated into the value of new innovations in standard QALY-based cost-utility models. They have a huge impact on patients' and caregivers' quality of life and on the efficiency of healthcare resource use more generally. In cases like MLD, PIPC would recommend system effects be incorporated into ICER's modeling.

Conclusion

PIPC urges ICER to reconsider the use of the QALY and several of its modeling choices given the severity of and population impacted by MLD.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care