PIPC Partnership to Improve Patient Care

August 13, 2024

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Dear Ms. Emond:

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 Transthyretin Amyloid Cardiomyopathy (ATTR-CM).

ATTR-CM is a historically underdiagnosed and potentially fatal disease. As treatment options become available, it is becoming increasingly diagnosed earlier, providing patients with an opportunity for enhanced quality of life. PIPC encourages ICER to consider the following comments.

ICER's models continue to oversimplify complex diseases in a manner that may misrepresent treatment effectiveness.

ICER's model categorizes patients into broad health states, missing marginal but meaningful improvements and likely underestimating the value of treatment. As PIPC has made clear in the past, in cost-effectiveness modeling it is problematic to oversimply a disease by using a model with too few health states. If treatment value is represented by movement of patients from a worse state to a better state, and too few states are identified or too crudely defined, then the number of people transitioning between states may appear to be low despite meaningful improvements within the overly broad health state, potentially underestimating the effectiveness of the treatment. ICER's model assumes a similar distribution of severity within states as across states.

People who remain in the state they started in at the end of a cycle may have a marginal improvement in outcomes that is not reflected in ICER's conclusions because they have not transitioned to the next defined health state. The model does not differentiate outcomes for people receiving treatment who improve but do not transition to a different health state from those who do not receive the treatment at all. Yet, marginal improvements can be vitally important to the patients in question and significantly improve their quality of life. When a model simplifies a complex disease down to a transition between three health states, as ICER's does, it is likely missing these marginal improvements and not capturing accurate treatment

value. This type of dichotomization or over-categorization of outcomes has been shown to lead to underestimation of treatment effects.[1,2]

ICER's report references the system effect of introducing treatment for transthyretin amyloid cardiomyopathy, but it does not include this in its modeling.

ICER's report makes note that the very existence of the first disease modifying treatment for ATTR-CM has led to an improved diagnosis rate. Early detection of disease leads to improved care, an element of value accrued to all ATTR-CM patients as the result of development of DMTs that is realized regardless of whether the patient is on the drug. This systems effect of treatments is something that has been discussed consistently in research literature[3,4]

Yet, this indirect marginal benefit that accrues to all ATTR-CM patients is not incorporated into standard cost-effectiveness modeling. Contrary to this element of value, ICER tries to make the case that *because* patients are now being diagnosed earlier and at less severe stages of disease, the net benefit of treatment could in fact be smaller than was seen in the trials for tafamidis, precisely because at the time these trials were conducted, the mean severity of a newly diagnosed patient was much higher. It is obvious that this was the case because no treatment existed, and doctors were not actively diagnosing ATTR-CM as often. We are very concerned that this type of overly simplistic value assessment methodology risks actively disincentivizing innovation to the detriment of patients. The fact that a new treatment has led to early diagnosis, better care and decreased severity of disease is evidence of its value for patients.

PIPC reiterates past comments and encourages ICER to evolve its value assessment methodology to include a wider, more complete, set of benefits so that cost-effectiveness models reflect the full scope of factors that represent value of new therapies for patients, health care providers and society at large. Academically many of these approaches have been widely accepted.[5,6] For

[1] Altman DG, Royston P. The cost of dichotomising continuous variables. Bmj. 2006 May 4;332(7549):1080.
[2] 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.
[3] Jena AB, Snider JT, Espinosa OD, Ingram A, Gonzalez YS, Lakdawalla D. How does treating chronic hepatitis C affect individuals in need of organ transplants in the United Kingdom?. Value in Health. 2019 Jun 1;22(6):669-76.
[4] 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 1;22(6 Spec No.):SP212-9.
[5] Lee D, McCarthy G, Saeed O, Allen R, Malottki K, Chandler F. The challenge for orphan drugs remains: three case studies demonstrating the impact of changes to NICE methods and processes and alternative mechanisms to value orphan products. PharmacoEconomics-Open. 2023 Mar;7(2):175-87.
[6] Reckers-Droog VT, Van Exel NJ, Brouwer WB. Looking back and moving forward: on the application of proportional shortfall in healthcare priority setting in the Netherlands. Health policy. 2018 Jun 1;122(6):621-9.

example, the elements of value of innovation,[7] risk-adjustment[8] and system effects[9] all apply here. Therefore, PIPC encourages ICER to rethink its modeling to include these elements.

ICER uses utilities derived from randomized controlled trial (RCT) data.

There are many limitations to using utility data derived solely from RCT settings. RCT populations are generally much healthier than real-world disease-specific populations.[10] There are always explicit and implicit exclusion criteria for recruitment into trial settings,[11] including age, the existence of co-morbidities[12] and levels of healthcare access and utilization, that make RCT populations rarely representative of real-world populations of need.[13, 14]

Additionally, utilities in RCTs tend to be inflated compared to non-RCT samples of patients[15] as patients in RCTs receive greater care and attention from healthcare professionals, which improve quality of life measures, even those not directly correlated to receiving the treatment. These discrepancies in utilities generated in RCTs versus real-world populations is well documented in research literature.[16]

ICER should reflect the heterogeneity of ATTR-CM subtypes either directly in the model or in parallel scenarios analyses.

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[7] Lakdawalla D, Malani A, Reif J. The insurance value of medical innovation. Journal of public economics. 2017 Jan 1;145:94-102.
[8] Lakdawalla DN, Phelps CE. Health technology assessment with diminishing returns to health: the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) approach. Value in Health. 2021 Feb 1;24(2):244-9.
[9] 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 1;22(6 Spec No.):SP212-9.
[10] Mitchell AP, Harrison MR, Walker MS, George DJ, Abernethy AP, Hirsch BR. Clinical trial participants with metastatic renal cell carcinoma differ from patients treated in real-world practice. Journal of oncology practice. 2015 Nov;11(6):491-7.
[11] Knepper, T.C. & McLeod, H.L. When will clinical trials finally reflect diversity? *Nature* **557**, 157–159 (2018).
[12] Unger, J.M., Hershman, D.L., Fleury, M.E. & Vaidya, R. Association of patient comorbid conditions with cancer clinical trial participation. *JAMA Oncol*. **5**, 326 (2019).
[13] Mishkin, G., Arnaldez, F. & Percy Ivy, S. Drivers of clinical trial participation—demographics, disparities, and eligibility criteria. *JAMA Oncol.* **5**, 305–306 (2019).
[14] Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials. 2015 Dec;16(1):1-4.
[15] Bradburn MJ, Lee EC, White DA, Hind D, Waugh NR, Cooke DD, Hopkins D, Mansell P, Heller SR. Treatment effects may remain the same even when trial participants differed from the target population. Journal of Clinical Epidemiology. 2020 Aug 1;124:126-38.
[16] Villines TC, Cziraky MJ, Amin AN. Awareness, knowledge, and utility of RCT data vs RWE: results from a survey of US cardiologists: real-world evidence in clinical decision making. Clinical Medicine Insights: Cardiology. 2020 Sep;14:1 179546820953410.

The model is constructed for a single population of ATTR-CM patients. There is a subtype of ATTR-CM patients who will also have comorbid ATTR-PN (polyneuropathy),[17] which makes the condition significantly more burdensome.[18] Given this increased burden, it would be likely that disease-modifying therapies (DMTs) would be more beneficial for this population and therefore significantly more cost-effective. ICER's model would be more accurate by running scenario analyses for those who have both conditions.

ICER continues to use the discriminatory QALY and other one-size fits all metrics.

Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions,[19] older adults and people with disabilities.[20] There is widespread recognition that the use of the QALY is discriminatory, reflected in laws that bar its use in government decision-making. The National Council on Disability (NCD), an independent federal agency advising Congress and the administration on disability policy, 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.[21] The recent nondiscrimination regulations governing Section 504 of the Rehabilitation Act also bar the use of discriminatory measures such as QALYs in decisions impacting access to care among entities receiving federal financial assistance.

We share the concerns of NCD about the equal value of life year gained (evLYG), a similar measure created by ICER to supplement the QALY. The evLYG is a simplistic fix attempting to address criticism that the QALY devalues life years lived with a disability, yet it fails to account for oversimplified measures of quality-of-life gains in expected life years and it does not account for any health improvements in extended life years. Like the QALY, the evLYG relies on average estimates based on generic survey data and obscures important differences in patients' clinical needs and preferences, particularly those with complex diseases and from underrepresented communities.[22] It assumes that people value life year gains more than quality

[17] Dohrn MF, Ihne S, Hegenbart U, et al. Targeting transthyretin—Mechanism-based treatment approaches and future perspectives in hereditary amyloidosis. *J Neurochem.* 2021;156(6):802818.
[18] Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail.* 2019;12(9), e006075.
[19] 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.
[20] 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.
[21] https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf
[22] DiStefano MJ, Zemplenyi A, Anderson KE, Mendola ND, Nair KV, McQueen RB. Alternative approaches to measuring value: an update on innovative methods in the context of the United States Medicare drug price

of life improvements, giving a lower value to health interventions for patient populations that have a lower life expectancy or fewer life years gained from treatment, which may include people with disabilities, underlying chronic conditions, older adults, and certain communities of color.[23] With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain.

Conclusion

ICER continues to rely on dated and simplistic modeling structures that do not provide a clear picture of real value the patient. We encourage ICER to revise its model to include more elements of value and better methods to meaningfully reflect patient experience on treatment.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

negotiation program. Expert Rev Pharmacoecon Outcomes Res. 2024 Feb;24(2):171-180. doi: 10.1080/14737167.2023.2283584. Epub 2024 Jan 25. PMID: 37961908.

[23] Mike Paulden, Chris Sampson, James F. O'Mahony, Eldon Spackman, Christopher McCabe, Jeff Round, Tristan Snowsill, Logical Inconsistencies in the Health Years in Total and Equal Value of Life-Years Gained, Value in Health, Volume 27, Issue 3, 2024, Pages 356-366.